21 July 2016
EMA/630770/2016
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Invented name: Ameluz

International non-proprietary name: 5-aminolevulinic acid

Procedure No. EMEA/H/C/002204/II/0020

Marketing authorisation holder (MAH): Biofrontera Bioscience GmbH

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

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List of abbreviations

∞	infinity
5-FU	5-fluorouracil
AK	actinic keratosis
ALA	amino-levulinic acid
BCC	basal cell carcinoma
BMI	body mass index
χ^2	chi square
C	Caucasian
C	carbon
CI	confidence interval
CR	clearance rate
CSR	clinical study report
eg	*exempli gratia*, for example
F	women
FAS	full-analysis set
HPLC-FD	high-liquid performance chromatography with fluorescence detection
HPLC-MS/MS	high-liquid performance chromatography with tandem mass spectrometry
ie	*id est*, that is
ITT	intent-to-treat
LED	light emitting diode
LLOQ	lower limit of quantification
M	men
MAL	methyl-amino-levulinate
MedDRA	Medical Dictionary for Regulatory Activities
n	number
N/A	not applicable
NMSC	mon-melanoma skin cancer
NR	not reported
$^1O_2$	singlet oxygen
OECD	Organisation for Economic Co-operation and Development
P	probability
PDT	photodynamic therapy
PK	pharmacokinetic
PP	per-protocol
PPS	per-protocol set
PpIX	protoporphyrin IX
r	randomized
ROS	reactive oxygen species
SCC	squamous cell carcinoma
SD	standard deviation
vITT	valid for intent-to-treat analysis
vs	*versus*, as opposed to
BF-200	*Designation of the nanoemulsion contained in the topical gel formulation*
AMELUZ 10% gel	*Designation of the nanoemulsion based gel formulation containing 10 % of 5-aminolevulinic acid hydrochloride (equivalent to 78 mg/g of 5-aminolevulinic acid)*
Target area A	*face and forehead*
Target area B	*bald scalp*

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Biofrontera Bioscience GmbH submitted to the European Medicines Agency on 9 December 2015 an application for a variation.

The following variation was requested:

Variation requested		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of Indication to include treatment of actinic keratosis of mild to moderate severity on the face and scalp (Olsen grade 1 to 2) and of field cancerization based on the phase III clinical study ALA-AK-CT007. As a consequence, sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC are updated. Package Leaflet is updated accordingly. In addition, the marketing authorisation holder (MAH) took the opportunity to make minor editorial changes in the SmPC and Package Leaflet.

Information on paediatric requirements

Not applicable.

Article 8 does not apply as the authorised medicinal product is not protected by a supplementary protection certificate under Regulation (EC) No 469/2009 or by a patent which qualifies for the granting of the supplementary protection.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Scientific advice

The MAH did not seek Scientific Advice at the CHMP.

1.2. Steps taken for the assessment of the product

The Rapporteur appointed by the CHMP was:

Rapporteur: Harald Enzmann

Timetable	Actual dates
Submission date	9 December 2015
Start of procedure:	3 January 2016
CHMP Rapporteur Assessment Report	26 February 2016
CHMP members comments	21 March 2016
Updated CHMP Rapporteur(s) (Joint) Assessment Report	24 March 2016
Request for supplementary information (RSI)	1 April 2016
MAH responses to the RSI	22 April 2016
Restart of the procedure	25 April 2016
CHMP Rapporteur Assessment Report on MAH's responses	24 May 2016
PRAC Rapporteur Assessment Report on MAH's responses	25 May 2016
PRAC members comments	1 June 2016
Updated PRAC Rapporteur Assessment Report on MAH's responses	2 June 2016
PRAC Outcome	9 June 2016
CHMP members comments	13 June 2016
Updated CHMP Rapporteur Assessment Report on MAH's responses	16 June 2016
2nd Request for supplementary information (RSI)	23 June 2016
MAH responses to the 2nd RSI	28 June 2016
Restart of the procedure	29 June 2016
CHMP Rapporteur Assessment Report on MAH's responses to the 2nd RSI	7 July 2016
PRAC Rapporteur Assessment Report on MAH's responses to the 2nd RSI	7 July 2016
CHMP members comments	11 July 2016
PRAC members comments	11 July 2016
Updated PRAC Rapporteur Assessment Report on MAH's responses to the 2nd RSI	15 July 2016
Updated CHMP Rapporteur Assessment Report on MAH's responses to the 2nd RSI	15 July 2016
Opinion	21 July 2016

2. Scientific discussion

2.1. Introduction

Actinic keratosis (AK) is an ultraviolet-light-induced lesion of the skin that can remain unchanged, resolve without further treatment or may progress to invasive squamous cell carcinoma. It is by far the most common lesion with malignant potential to arise on the skin. AK is mostly seen in fair-skinned persons on skin areas that have had long-term sun exposure (Salasche, 2000). Regions with higher ultraviolet exposure have a higher prevalence of AK. In Europe, a prevalence of 15% in men and 6% in women has been documented. Over the age of 70 years, 34% of men and 18% of women were found to have AK (Memon et al, 2000). Following topical application of ALA (5-aminolevulinic acid), the substance is metabolized to PpIX, a photoactive compound which accumulates intracellularly in the treated actinic keratosis lesions. PpIX is activated by illumination with red light of a suitable wavelength and energy. In the presence of oxygen, reactive oxygen species are formed. The latter causes damage to cellular components and eventually destroys the target cells. Red-light illumination was chosen since light with longer wave lengths penetrates deeper into the tissue.

Treatment for AK is chosen based on several aspects such as age of the patient at diagnosis, previous occurrence of skin cancer, presence of the lesion(s), and the patient's tolerability of the treatment. The treatment options consist of either surgical destruction for well-defined lesions of the skin, topical medicinal products and photodynamic therapy. Current medicinal products approved for AK include 5-fluorouracil, imiquimod and ingenol mebutate. PDT requires 3 components: (1) a photosensitizer, (2) light with a sufficient amount of energy at a suitable spectrum of wavelengths, and (3) oxygen. In PDT light energy is transferred by the photosensitizer to oxygen, leading to the formation of reactive oxygen species (ROS). ROS oxidize cell membranes and other cellular compounds, causing necrosis or apoptosis of targeted cells. Ameluz (with 5-aminolevulinic acid as active ingredient) belongs to the pharmacological class of medications called "photodynamic therapy photosensitizers".

BF-200 ALA 10% (Ameluz) is a non-sterile, topical formulation of 10% 5-aminolevulinic acid hydrochloride in a gel-matrix with nanoemulsion. BF-200 ALA 10% contains 10% ALA as hydrochloride salt, equaling 7.8% of the free acid. BF-200 ALA 10% is used in combination with red light photodynamic therapy. 5-Aminolevulinic acid (ALA) is a delta-amino acid and occurs as an endogenous molecule of the heme biosynthesis pathway in almost every cell in humans, animals and plants. ALA functions as a pro-drug and is metabolized to the photoactive substance protoporphyrinIX (PpIX) in mitochondria. PpIX, a photoactive compound, accumulates intracellularly in the treated actinic keratosis lesions. PpIX is activated by illumination with red light of a suitable wavelength and energy. In the presence of oxygen, reactive oxygen species are formed. The latter cause damage of cellular components and eventually destroys the target cells. Many actinic keratoses do not appear solitarily but in an area exceeding 4 cm2 (field cancerization). Field cancerization describes areas including actinic keratosis lesions and chronically photo-damaged fields. Data from a new phase III trial (ALA-AK-CT007) is provided to support the efficacy and safety of the treatment in patients with AK and field cancerisation.

The MAH has applied for an extension of the indication as follows:

Ameluz is indicated for treatment of actinic keratoses of mild to moderate ~~intensity~~ severity on the face and scalp (Olsen grade 1 to 2; see section 5.1) and of field cancerization.

One session of photodynamic therapy should be administered for single or multiple lesions or entire fields with cancerization. Actinic keratosis lesions or fields should be evaluated three months after treatment. Treated lesions or fields that have not completely resolved after 3 months shall be retreated.

2.2. Non-clinical aspects

No new relevant non-clinical data have been submitted in this application, which was considered acceptable by the CHMP.

2.2.1. Ecotoxicity/environmental risk assessment

The MAH did not submit an ERA. The extended indication is not expected to lead to a significant increase in environmental exposure further to the use of 5-aminolevulinic acid. Hence, the extension of the indication is not likely to pose a significant risk to the environment. 5-aminolevulinic acid should be used according to the precautions stated in the SmPC in order to minimise any potential risks to the environment. Therefore, a standard disposal advice was updated in section 6.6 of the SmPC to add the following wording "Any unused medicinal product or waste material should be disposed of in accordance with local requirements".

2.2.2. Discussion on non-clinical aspects

The lack of non-clinical data to support the extension of the indication is acceptable as the condition and patient population is the same and the indication has not substantially changed. Therefore, no update to section 5.3 of the SmPC was proposed. The SmPC has been updated in section 6.6 concerning the disposal of the product in accordance with local requirements.

2.2.3. Conclusion on the non-clinical aspects

The justification for not submitting an ERA in this application is acceptable as the data suggest that there will be no significant increase in environmental exposure to 5-aminolevulinic acid as the target population in the indication is the same as previously. Hence, 5-aminolevulinic acid is not expected to pose an increased risk to the environment. The lack of non-clinical studies is considered justified.

2.3. Clinical aspects

2.3.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant. A GCP-Inspection in centre 03 with no critical and major findings was performed on 8 Apr to 9 Apr 2015 by the Regional Administrative Authority, Munich (Germany).

The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies

Study Number, Location	Study Objective - Main inclusion criteria	Study design	IMPs (PDT lamp)	Duration of Treatment and follow-up	N Enrolled/ planned
ALA-AK-CT002 Germany, Austria, Switzerland - 26 centres 17Apr2008-11May2010 Completed	To compare the efficacy of PDT with BF-200 ALA vs. the marketed product MAL cream (Metvix) and placebo in the treatment of AK. Patients with 4 to 8 AK target lesions 0.5 to 1.5 cm diameter of mild to moderate severity a on the face or bald scalp.	Phase III, randomized, multinational, reference therapy controlled and placebo controlled, observer blind to reference therapy and double blind to placebo, parallel group study (ratio 3:3:1).	- BF-200 ALA 10% - Vehicle - MAL cream (Aktilite CL 128, 630 nm), Omnilux PDT, 633 nm) Waldmann PDT 1200L, 600-750 nm) (Hydrosun/ PhotoDyn, 580-1400 nm).	Up to two PDTs; 12 weeks after the first PDT, non-responders or partial responders were to be retreated. Follow-up was 6 months and 12 months after the last PDT.	571 / 616
ALA-AK-CT005 - Germany - 2 centres 13Jun2013-19Oct2013	To investigate the skin sensitization potential of Ameluz (BF 200 ALA 10%) and its vehicle after repeated topical application in male and female subjects aged 18 to 85 years with healthy skin.	Phase I, two-centre, randomized, double blind trial, intraindividual comparison of treatments.	- BF-200 ALA 10% - Vehicle	Treatment (200 µl in Finn Chambers) over 48 hours (72 h weekends) 3 times weekly for 3 weeks during induction and single application, for 48 h challenge and re challenge phases as applicable.	220 /200
ALA-AK-CT006 - Germany - 1 centre 11Jul2013-16Dec2013	To obtain baseline adjusted plasma concentration-time curves for ALA and PpIX after a single treatment with Ameluz (BF 200 ALA 10%) in subjects with ≥ 10 AK lesions on face or forehead with a maximum of 2 illumination areas with each lesion being not more than 2 mm thick with a side margin of at least 5 mm (maximal use).	Phase I, Single centre, non-randomized, open-label, placebo controlled, fixed sequence, 2-treatment, intra-individual comparison study.	- BF-200 ALA 10% - Vehicle (BF-RhodoLED, 635 nm)	Each patient will receive a PDT after application of placebo (Period 1) and after application of ALA (Period 2) with a washout period of at least 1 week between treatments. Approximately 20 cm² were treated applying sequentially one tube (2 g) vehicle and BF200 ALA 10% gel, respectively. Follow-up was within 7±1 days after last PDT	12 /12

ALA-AK-CT007 Germany -7 centres 27Aug2013- 24Apr2015 Completed	The primary objective was to compare the efficacy of BF-200 ALA with placebo, for the field-directed treatment of AK with PDT. Patients with 4 to 8 AK target lesions 0.5 to 1.5 cm diameter of mild to moderate severity a on the face or bald scalp located within 1-2 fields of an overall size of ca. 20 cm^2.	Phase III, multicenter, randomized, double blind, placebo controlled, parallel group (2:1 ratio) study.	- BF-200 ALA 10% - Placebo/vehicle (BF-RhodoLED, 635 nm).	Up to two PDTs. Twelve weeks after the first PDT, non-responders or Partial responders were to be retreated. Follow-up was 6 and 12 months after last PDT.	87 / 84

2.3.2. Pharmacokinetics

Absorption

Study ALA-AK-CT006: A single center, non-randomized, open-label, placebo-controlled, fixed sequence Phase I study to evaluate the pharmacokinetics of 5-aminolevulinic acid (ALA) in 12 patients with actinic keratosis following topical application of a gel formulation containing 78 mg/g ALA (Ameluz) under maximal use conditions when using photodynamic therapy.

The primary objective of the study was to obtain baseline-adjusted plasma concentrations-time curves for ALA and its metabolic product protoporphyrin IX (PpIX) after a single treatment with ALA in patients with actinic keratosis under maximal use conditions.

The secondary objectives of the study included:

- Evaluation of pharmacokinetic parameters of ALA: AUC_{0-t}, $AUC_{0-\infty}$, and C_{max} derived from baseline-adjusted plasma concentrations (if data permitted).
- Evaluation of pharmacokinetic parameters of ALA: t_{max}, $t_{1/2}$, and λ_z derived from unadjusted plasma concentrations (if data permitted) because baseline-adjustment had no influence on these estimates.
- Assessment of safety and tolerability of ALA under maximal use conditions

Patients were included with a confirmed actinic keratosis of mild to moderate intensity (Olson Grade 1 and 2) between 18 and 85 years (inclusive) with at least 10 actinic keratosis lesions on face or forehead in a total topical treatment area of approximately 20 cm^2 with a maximum of 2 illumination areas with each lesion being not more than 2 mm thick and having a side margin of at least 5 mm.

ALA was applied topically as a film of approximately 1 mm thickness over the treatment area of approximately 20 cm^2. Each patient received a photodynamic therapy after application of placebo (Period 1) and after application of ALA (Period 2) with a washout period of 7 days.

The primary endpoint was baseline-adjusted plasma concentrations of ALA and PpIX that were used for obtaining baseline corrected plasma concentrations-time curves. The secondary endpoints were baseline-adjusted AUC_{0-t}, baseline-adjusted $AUC_{0-\infty}$, baseline-adjusted C_{max}, t_{max}, $t_{1/2}$, and λ_z of ALA.

Further endpoints analysed were baseline-adjusted AUC_{0-t}, baseline-adjusted $AUC_{0-\infty}$, baseline-adjusted C_{max}, t_{max}, $t_{1/2}$, and λ_z of PpIX and the following pharmacokinetic characteristics were determined unadjusted C_{max} and baseline-adjusted t_{max} of ALA and PpIX. Safety was assessed by evaluating physical examination, blood pressure and pulse rate, 12-lead electrocardiogram, local and overall tolerability, pain assessment, safety laboratory and adverse events.

All patients showed ALA concentrations above LLOQ at all sampling time points. In most of the patients ALA was systemically absorbed, i.e., an obvious increase of ALA concentrations was observed after application of the ALA gel compared to baseline and the placebo gel. Maximum geometric mean ALA concentrations were reached at 3 h after application. There was low systemic absorption; the geometric mean of Cmax was about 2.5 times of the geometric mean of baseline concentrations (41.18 ng/mL vs 17.28 ng/mL). Baseline-adjusted maximum concentrations (C_{max}) were 4.47 ng/ml (range 1.4 – 6.94 ng/ml) following placebo and 21.56 ng/ml (range 4.76 – 77.53 ng/ml) following Ameluz. Thereafter, ALA was eliminated quickly from plasma returning to approximate baseline levels within 10 h after application. Baseline-adjusted total (AUC_{0-t}) and maximum (C_{max}) exposure to ALA was increased after application of the ALA gel compared to the placebo gel.

In one patient baseline concentrations of ALA were about 3-fold higher in Period 2 compared to Period 1 (placebo gel). Descriptive statistics of plasma concentrations and pharmacokinetic parameters of ALA excluding this patient showed similar results as compared to the analysis including this patient. There was only little systemic absorption, geometric mean of C_{max} was about 2.5 times of the geometric mean of baseline concentrations (with and without the outlier patient).

PpIX

Concentrations of metabolite PpIX were generally low in all patients. Four patients showed concentrations BLLQ at all post-dose sampling time points. Most of the other patients showed concentrations BLLQ incidentally. In none of the patients, an obvious difference of PpIX concentrations was observed after application of the ALA gel compared to baseline and the placebo gel, i.e. metabolism of ALA to PpIX was not increased under maximal use conditions.

2.3.3. Discussion on clinical pharmacology

The study ALA-AK-CT006 is deemed adequate in terms of the overall study design, PK measures and the patients selected patients. ALA was systemically absorbed, i.e., baseline-adjusted total (AUC_{0-t}) and maximum (C_{max}) exposure to ALA was increased after application of Ameluz compared to the vehicle. Maximum concentrations were observed at 3 h after application and systemic absorption was low. Thereafter, ALA was eliminated quickly from plasma returning to approximate baseline levels within 10 h after application. In addition, concentrations of metabolite PpIX were also found to be low in all patients. The MAH provided literature data which supported the overall conclusions (data not shown). Hence, the SmPC section 5.2 has been updated with information that with the maximal use of Ameluz, plasma concentration of Ameluz was still within the normal range of reported endogenous ALA concentrations.

2.3.4. Conclusions on clinical pharmacology

There is no relevant increase to the plasma concentration of either ALA or PpIX when the product is used at maximal concentration. Considering that treatment of AK according to the new indication will cover a wider surface area, with potentially repeated use, this information confirms that there should be no potential implications derived by the exposure based on the extended use of the product. This information has been adequately reflected in section 5.2 of the SmPC.

2.4. Clinical efficacy

2.4.1. Main studies

ALA-AK-CT007: A randomized, double-blind, phase III, multi-center study to evaluate the safety and efficacy of BF-200 ALA (Ameluz) versus placebo in the field directed treatment of mild to moderate actinic keratosis with photodynamic therapy (PDT) when using the BF-RhodoLED lamp

Methods

Study participants

Main inclusion criteria

- Males or females between 18 and 85 years of age (inclusive).
- Presence of 4 to 8 clinically confirmed AK target lesions of mild to moderate intensity within 1-2 treatment fields in the potential treatment area face and forehead (treatment area A) or bald scalp (excluding eyes, nostrils, ears, and mouth) (treatment area B), i.e. AK grade 1 and 2 according to Olsen et al. 1991[1]. AK lesions had to be discrete and measurable; the lesions had to be located within 1-2 fields of an overall size of approximately 20 cm^2.
- Diameter of each AK lesion between 0.5 cm and 1.5 cm.
- Confirmation of AK by biopsy at screening.
- Willingness to undergo a second biopsy at the end-of-study visit (12 weeks after the last PDT).
- Free of significant physical abnormalities (e.g. tattoos, dermatoses) in the potential treatment area that may complicate examinations or final evaluations.
- Willingness to stop the use of moisturizers and any other topical treatments within the treatment area.
- Accepting to abstain from extensive sunbathing and the use of a solarium during the period of the clinical visits. Patients experiencing sunburn within the treatment areas could not be included until they had fully recovered.
- Good general health and/or stable health condition, as confirmed by a physical examination and medical history.
- Healthy patients and patients with clinically stable medical conditions including, but not limited to, the following diseases: controlled hypertension, diabetes mellitus type II, hypercholesterolemia, and osteoarthritis; patients could be included into the study if the medications taken for the treatment of the disease did not match an exclusion criterion or were not specified as prohibited concomitant medication.
- Negative pregnancy test at screening.
- Effective contraception in women of childbearing potential.

Main exclusion criteria

- History of hypersensitivity to 5-ALA or any ingredient of BF-200 ALA.
- Current treatment with immunosuppressive therapy.

[1] Olsen et al., A double-blind, vehicle-controlled study evaluating masoprocol cream in the treatment of actinic keratoses on the head and neck. J Am Acad Dermatol. 1991 May;24(5 Pt 1):738-43

- Presence of porphyria.
- Hypersensitivity to porphyrins.
- Presence of photodermatoses.
- Presence of other malignant or benign tumors of the skin within the treatment area (e.g. malignant melanoma, basal cell carcinoma [BCC] or squamous cell carcinoma [SCC]) within the last 4 weeks.
- Confirmed diagnosis of SCC for the representative lesion by screening biopsy.
- Presence of an inherited or acquired coagulation defect.
- Start of treatment with phototoxic or photoallergic drugs within 8 weeks prior to screening.
- Clinically relevant cardiovascular, hepatic, renal, neurologic, endocrine or other major systemic diseases making implementation of the protocol or interpretation of the study results difficult.
- Evidence of clinically significant, unstable medical conditions such as:
    - Metastatic tumour or tumor with high probability of metastasis,
    - Cardiovascular disease (New York Heart Association [NYHA] class III, IV),
    - Immunosuppressive condition,
    - Hematologic, hepatic, renal, neurologic, or endocrine condition,
    - Collagen-vascular condition,
    - Gastrointestinal condition.
- Any topical treatment within the treatment area within 12 weeks before PDT-1.
- Topical treatment with ALA outside the treated field(s)during participation in the study
- Topical treatment with methyl-aminolevulinic acid (MAL) during participation in the study
- Topical treatment with immunomodulatory agents (e.g. imiquimod, ingenol mebutate) 4 weeks prior to the first PDT session
- Any of the specified systemic treatments within the designated period before PDT-1

Treatments

BF-200 ALA packed in tubes (two tubes per patient) were assigned to allow for retreatment, if necessary. Each tube was sufficient to cover 1-2 fields of approximately 20 cm^2 in total. The treatment field(s) were prepared for drug application by degreasing (using ethanol or isopropanol) and subsequently removing all scabs, crusts, and hyperkeratotic parts (using curettage). ALA was applied over 1-2 fields of approximately 20 cm^2 in total, allowed to dry for approximately 10 minutes, and covered with occlusive tape material for 3 h. Thereafter, any remnants of the applied formulation were removed carefully and PDT illumination using the BF-RhodoLED lamp was administered. Patients with non-responding AK lesions were retreated with the same medication after 12 weeks.

A placebo (a nanoemulsion gel formulation but without the active ingredient) was assigned to each patient, and administered in the same way as the BF-200 ALA.

Planned duration was 1 day to 12 weeks: BF-200 ALA or placebo was administered for the first PDT session (PDT-1) after all screening procedures had been performed. A second PDT session (PDT-2) with BF-200 ALA or placebo was performed 12 weeks later if there were lesions that were not completely cleared.

For all patients, 2 FU visits at 6 and 12 months after the last PDT were scheduled.

Objectives

The primary objective was to compare the efficacy of BF-200 ALA with placebo for the field-directed treatment of mild to moderate actinic keratosis (AK) with PDT when using the BF-RhodoLED lamp.

The secondary objectives were: To evaluate the safety and secondary efficacy parameters related to BF-200 ALA for field-directed treatment of AK with PDT when using the BF-RhodoLED lamp in a multicenter, randomised, double-blind, placebo-controlled, parallel group (2:1 ratio) with 84 patients were planned to be randomized.

Outcomes/endpoints

Primary efficacy endpoint: Overall patient complete response (complete clearance of all treated lesions) assessed 12 weeks after the last PDT. An overall complete responder was defined as a patient in whom all treated AK lesions were cleared (Olsen score of 0) after the last PDT, i.e. after PDT-1 or after PDT-2 if re-treatment was performed.

Secondary efficacy endpoints:

- Patient histopathological confirmed response (HCR) rate.
- Patient complete response (complete clearance of all treated lesions) assessed 12 weeks after PDT-1.
- Lesion complete response (complete clearance of all treated lesions) assessed 12 weeks after the last PDT.
- Patient partial response (complete clearance of at least 75% of the treated lesions) assessed 12 weeks after the last PDT.
- Reduction of total lesion area (the size of all treated lesions added up) per patient 12 weeks after the last PDT compared to baseline.
- The overall cosmetic outcome 12 weeks after the last PDT. The cosmetic outcome assessments were based on skin quality assessments at 12 weeks after the last PDT, which were reported by the investigator on a 4-point scale ranging from 0 (none) to 3 (severe). The cosmetic outcome was defined on a 5-point scale taking into account the investigator's ratings of the skin quality parameters.
- Patient complete response (complete clearance of all treated lesions) assessed 3-4 weeks after PDT-1, 3-4 weeks and 12 weeks after PDT-2, and 3-4 weeks after last PDT.
- Patient partial response (complete clearance of at least 75% of the treated lesions) assessed 3-4 weeks and 12 weeks after PDT-1, 3-4 weeks and 12 weeks after PDT- 2, and 3-4 weeks after last PDT.
- Lesion complete response (completely cleared individual lesions) assessed 3-4 weeks and 12 weeks after PDT-1, 3-4 weeks and 12 weeks after PDT-2, and 3-4 weeks after last PDT.
- Reduction of total lesion area (the size of all treated lesions added up) per patient assessed 3-4 weeks and 12 weeks after PDT-1, 3-4 weeks and 12 weeks after PDT- 2, and 3-4 weeks after last PDT.
- Number of new lesions in the treated field(s) assessed 12 weeks after PDT-1 and 12 weeks after the last PDT.
- Change in skin quality assessments 12 weeks after the last PDT compared to baseline.

- Patient's satisfaction.

Safety

- Treatment-emergent adverse events (TEAEs) and serious adverse events (SAEs).
- Local skin reactions at the treatment area assessed by the investigators.
- Local discomfort and pain reported by patients during illumination.
- New lesions (AK, non-melanoma skin cancer (NMSC), melanoma in the treatment area).
- Vital signs (blood pressure and pulse rate).
- Laboratory (hematology, serum chemistry, and urinalysis).
- Physical examinations.

Sample size

A sample size of 56 patients in the active treatment arm and 28 patients in the placebo arm ensured a power of more than 90% to demonstrate a statistically significant difference in response rates with a Fisher's exact test in the FAS. This estimate was based on the assumption of an expected placebo response rate of 27.5% (based on a previous study), an expected BF-200 ALA response rate of 72.5%, and a rate of missing or non-evaluable observations that cannot be imputed of 10%. As it cannot be excluded that these cases are missing not at random and related to an unfavourable outcome, these patients were considered non-responders. A randomization ratio of BF-200 ALA and placebo of 2:1 was selected. The sample size is a multiple of 12 to stratify randomization by study site assuming 12 patients per site.

Randomisation

Patients were randomised in a 2:1 allocation ratio of active treatment to control. Randomisation was stratified by center. Six to 18 patients were to be enrolled per site (up to 24 patients with prior permission). The randomisation schedule was automated for random assignment. The randomisation was performed in blocks to facilitate attainment of a homogeneous distribution of treatment groups and block size was not revealed before study completion.

Blinding (masking)

The study was performed in a double-blind fashion. Active treatment and placebo were manufactured and packaged to ensure blinding. To guarantee the blind status of the investigator assessing efficacy after each PDT session, a second investigator or delegated person performed the PDT and conducted all safety evaluations during the PDT and the telephone call 1 week after PDT.

Statistical methods

The primary null hypothesis was that the overall complete responder rate assessed 12 weeks after the last PDT for patients treated with BF-200 ALA is equal to that of patients treated with placebo. Fisher's exact test was used to test the primary hypothesis on a significance level of 0.05 two-sided. The impact of missing data on the results were to be evaluated with sensitivity analyses if the number and frequency distribution of missing data indicated a possibly substantial influence on primary or secondary efficacy results (e.g. a worst-case analysis).

No interim analysis was foreseen or performed.

A hierarchic test procedure was used for confirmatory hypothesis testing of secondary variables measured during the double-blind treatment period. These tests were to be performed only after the test of the primary efficacy variable was passed and were conducted in a strictly pre-defined order to

ensure the family-wise error rate. Hypothesis testing in the pre-defined order was to stop once the first non-significant test-result was obtained. The secondary endpoints included different response variables (patient based histopathological confirmed response rate, patient based complete response, lesion based complete response, patient based partial response (at least 75% of lesions)), analysed with similar methods as the primary endpoint, reduction of total lesion area per patient, evaluated by analysis of covariance (ANCOVA) with factor treatment and baseline total lesion area as covariate, and overall cosmetic outcome, analysed with a Wilcoxon-Mann-Whitney test. Secondary endpoints were assessed 12 weeks after last PDT. Primary and secondary efficacy analyses were performed on the full analysis set.

Exploratory subgroups analyses in pre-defined subgroups of interest were performed by analysis in strata, Cochran-Mantel-Haenszel tests adjusted for subgroups and by logistic regression.

Continuous data was summarised by using descriptive statistics. Categorical variables were summarised by using frequency and percentages. Laboratory values were classified as normal or abnormal according to the laboratories normal ranges and indicated as clinically significant or not clinically significant by the investigator, and shift tables illustrating changes with respect to the normal ranges between baseline and endpoint were also presented. Vital signs focused on change from baseline to the scheduled time points after baseline. All other safety variables were analysed descriptively. The safety analyses were performed for the safety analysis set.

Results

Recruitment

This study was conducted in 7 centres in Germany. Of 94 patients enrolled in this study, 87 patients were randomised (55 patients to BF-200 ALA and 32 patients to placebo); the remaining 7 patients were excluded from the study due to screening failures.

Conduct of the study

Seven randomized patients prematurely discontinued the clinical part of the study: 5 patients due to patient's decision (all in the placebo group) and 2 patients were lost to follow-up (one patient in each group). In total, 10 patients included in the FAS had at least one major protocol deviation and were excluded from the PP population. A summary of major protocol deviations is presented in Table 1.

Table 1: Major protocol deviations – FAS

Protocol deviation	Number of patients, n (%)		
	Placebo	BF-200 ALA	Total
At least one major protocol deviation	5 (15.6)	5 (9.1)	10 (11.5)
No AK lesion assessment available after the first or, if re-treated, after the 2nd PDT	1 (3.1)	0 (–)	1 (1.1)
Missing evaluation of 2nd biopsy at end-of-study visit or diagnosis of BCC or SCC	5 (15.6)	1 (1.8)	6 (6.9)
Concomitant medications or therapies which might have an impact on efficacy or safety analyses	0 (–)	2 (3.6)	2 (2.3)
Not treated with BF-RhodoLED lamp	0 (–)	2 (3.6)	2 (2.3)

AK= actinic keratosis; BCC= basal cell carcinoma; PDT= photodynamic therapy; SCC= squamous cell carcinoma.

Baseline data

Table 2: Demographic characteristics - FAS

Variable		Placebo N=32	BF-200 ALA N=55	Total N=87
Sex				
Male	n (%)	29 (90.6)	50 (90.9)	79 (90.8)
Female	n (%)	3 (9.4)	5 (9.1)	8 (9.2)
Age	Mean (SD)	71.0 (6.44)	71.9 (6.42)	71.6 (6.41)
	Median (Min-Max)	72.0 (51–84)	73.0 (56–84)	72.0 (51–84)
Age group (years)				
≤65 years	n (%)	6 (18.8)	9 (16.4)	15 (17.2)
>65 years	n (%)	26 (81.3)	46 (83.6)	72 (82.8)
Race				
White	n (%)	32 (100)	55 (100)	87 (100)
Ethnicity				
Not Hispanic or Latino	n (%)	32 (100)	55 (100)	87 (100)
Weight (kg)[a]	Mean (SD)	82.9 (12.55)	82.6 (10.80)	82.7 (11.41)
	Median (Min-Max)	81.9 (64–115)	83.4 (54–110)	82.8 (54–115)
Height (cm)[a]	Mean (SD)	174.7 (7.99)	175.7 (7.96)	175.3 (7.94)
	Median (Min-Max)	175.0 (156–192)	176.5 (156–199)	175.0 (156–199)
Body mass index (kg/m^2)[a]	Mean (SD)	27.1 (3.30)	26.8 (2.95)	26.9 (3.07)
	Median (Min-Max)	26.9 (20–34)	26.9 (20–34)	26.9 (20–34)

[a] Data for one patient in the BF-200 ALA group are missing; Max= maximum; Min= minimum; n = number of patients; N= number of patients in a treatment group; SD= standard deviation.

Table 3: History of skin cancer and skin type at baseline - FAS

Variable	Number of patients, n (%)		
	Placebo N=32	BF-200 ALA N=55	Total N=87
Family history of skin cancer			
No family history	30 (93.8)	50 (90.9)	80 (92.0)
Basal cell carcinoma	1 (3.1)	1 (1.8)	2 (2.3)
Dysplastic naevus syndrome	0 (–)	0 (–)	0 (–)
Skin cancer (not specified)	0 (–)	1 (1.8)	1 (1.1)
Squamous cell carcinoma of skin	0 (–)	0 (–)	0 (–)
Melanoma	0 (–)	1 (1.8)	1 (1.1)
Other	1 (3.1)	3 (5.5)	4 (4.6)
Fitzpatrick Skin Typing Score			
I (0-7)	0 (–)	1 (1.8)	1 (1.1)
II (8-16)	12 (37.5)	28 (50.9)	40 (46.0)
III (17-24)	19 (59.4)	19 (34.5)	38 (43.7)
IV (25-30)	1 (3.1)	6 (10.9)	7 (8.0)
V to VI (>30)	0 (–)	1 (1.8)	1 (1.1)

N= number of patients in a treatment group.

Table 4: Disease history and AK lesion characteristics at baseline - FAS

		Placebo N=32	BF-200 ALA N=55	Total N=87
Years since first diagnosis of AK	Mean (SD)	5.9 (4.42)	5.4 (3.68)	5.6 (3.95)
	Median (Min-Max)	4.6 (0-15)	5.1 (0-17)	4.7 (0-17)
History of AK Therapy				
No previous therapy	n (%)	2 (6.3)	8 (14.5)	10 (11.5)
Non-surgical therapy	n (%)	15 (46.9)	18 (32.7)	33 (37.9)
Surgical therapy	n (%)	0 (–)	2 (3.6)	2 (2.3)
Non-surgical and surgical therapy	n (%)	15 (46.9)	27 (49.1)	42 (48.3)
Histological confirmation of AK diagnosis by KIN grade				
I	n (%)	9 (28.1)	7 (12.7)	16 (18.4)
II	n (%)	23 (71.9)	47 (85.5)	70 (80.5)
III	n (%)	0 (–)	1 (1.8)	1 (1.1)
Location of AK lesions				
Treatment area A	n (%)	17 (53.1)	32 (58.2)	49 (56.3)
Treatment area B	n (%)	14 (43.8)	22 (40.0)	36 (41.4)
Treatment area A and B	n (%)	1 (3.1)	1 (1.8)	2 (2.3)
Maximum Olsen Severity Grading				
Mild	n (%)	7 (21.9)	10 (18.2)	17 (19.5)
Moderate	n (%)	25 (78.1)	45 (81.8)	70 (80.5)
Severe	n (%)	0 (–)	0 (–)	0 (–)

AK= actinic keratosis; KIN= keratinocytic intraepithelial neoplasm; Max= maximum; Min= minimum; N= number of patients in a treatment group; n=number of patients, SD= standard deviation.

Table 5: Number of AK lesions at baseline - FAS

		Placebo N=32	BF-200 ALA N=55	Total N=87
AK lesions at baseline per patient	Mean (SD)	5.4 (1.16)	5.4 (0.99)	5.4 (1.05)
	Median (Min-Max)	5.0 (4-8)	5.0 (4-8)	5.0 (4-8)
AK lesions at baseline	n	173	298	471
AK lesions at baseline by treatment area				
Treatment area A	n (%)	93 (53.8)	175 (58.7)	268 (56.9)
Treatment area B	n (%)	80 (46.2)	123 (41.3)	203 (43.1)
AK lesions at baseline by Olsen Severity Grading and treatment area				
Mild				
Treatment area A	n (%)	38 (22.0)	70 (23.5)	108 (22.9)
Treatment area B	n (%)	23 (13.3)	36 (12.1)	59 (12.5)
Moderate				
Treatment area A	n (%)	55 (31.8)	105 (35.2)	160 (34.0)
Treatment area B	n (%)	57 (32.9)	87 (29.2)	144 (30.6)

AK= actinic keratosis; Max= maximum; Min= minimum; n= number of AK lesions; N= number of patients in a treatment group; SD= standard deviation.

Numbers analysed

Table 6: Number of patients by analysis set

Population	Number of patients, n (%)		
	Placebo	BF-200 ALA	Total
Safety analysis set	32 (100)	55 (100)	87 (100)
Full analysis set	32 (100)	55 (100)	87 (100)
Complete responder after PDT-1 set	3 (9.4)	34 (61.8)	37 (42.5)
Patients who received 2 PDTs set	24 (75.0)	21 (38.2)	45 (51.7)
Per protocol set	27 (84.4)	50 (90.9)	77 (88.5)
Complete responder after PDT-1 set	3 (9.4)	29 (52.7)	32 (36.8)
Patients who received 2 PDTs set	22 (68.8)	21 (38.2)	43 (49.4)

PDT= photodynamic therapy.

Of 84 patients who entered the FU phase, 80 patients had completed the clinical phase (54 patients in the BF-200 ALA group and 26 patients in the vehicle group). Another 4 of 7 patients withdrawn from the clinical phase were included in the FU. In the BF-200 ALA group, 49 patients were complete responders 12 weeks after the last PDT (33 patients 12 weeks after PDT1, and 16 patients 12 weeks after PDT2), in the vehicle group 7 patients were complete responders (3 patients 12 weeks after PDT1, and 4 patients 12 weeks after PDT2). 54 patients in the BF-200 ALA group and 26 patients of the vehicle group completed the FU. 4 patients (all in the vehicle group) prematurely discontinued the FU phase due to being lost to follow-up.

The database lock for the clinical phase was 3 September 2014.

Outcomes and estimation

Primary efficacy: Overall patient complete response 12 weeks after the last PDT

At 12 weeks after the last PDT, 50 (90.9%) patients in the BF-200 ALA group and 7 (21.9%) patients in the placebo group showed complete clearance of AK lesions.

Table 7: Patient complete response rate 12 weeks after last PDT - FAS

	Placebo	BF-200 ALA	Difference in % points to BF-200 ALA
N with data	32	55	
Responder, n (%)	7 (21.9)	50 (90.9)	69.0
95% CI	9.3; 40.0	80.0; 97.0	52.8; 85.2
p-value Fisher's exact test			<0.0001

CI= Confidence interval, Clopper-Pearson CIs; PDT= Photodynamic therapy; N= number of patients; n= number of responders

For all subgroups, overall patient complete response 12 weeks after last PDT and exploratory p-values and confidence intervals of the difference in responder rate between BF-200 ALA and placebo are summarized in Table 8.

Table 8: Patient overall complete response 12 weeks after last PDT by subgroup - FAS

Subgroups			Placebo	BF-200 ALA	Difference in % points to BF-200 ALA	p-value*
Maximum AK severity at baseline	Grade I	n/N (%)	5/7 (71.4)	10/10 (100)	28.6	
		95% CI	29.0; 96.3	69.2; 100.0	–4.9; 62.0	0.1544
	Grade II	n/N (%)	2/25 (8.0)	40/45 (88.9)	80.9	
		95% CI	1.0; 26.0	75.9; 96.3	66.8; 94.9	<0.0001
Age	>65 years	n/N (%)	6/26 (23.1)	42/46 (91.3)	68.2	
		95% CI	9.0; 43.6	79.2; 97.6	50.1; 86.4	<0.0001
	≤65 years	n/N (%)	1/6 (16.7)	8/9 (88.9)	72.2	
		95% CI	0.4; 64.1	51.8; 99.7	36.0; 100.0	0.0110
Sex	male	n/N (%)	7/29 (24.1)	45/50 (90.0)	65.9	
		95% CI	10.3; 43.5	78.2; 96.7	48.2; 83.5	<0.0001
	female	n/N (%)	0/3 (0.0)	5/5 (100)	100.0	
		95% CI	0.0; 70.8	47.8; 100.0	100.0; 100.0	0.0179
Skin type group	I to III	n/N (%)	7/31 (22.6)	45/48 (93.8)	71.2	
		95% CI	9.6; 41.1	82.8; 98.7	54.9; 87.4	<0.0001
	IV or more	n/N (%)	0/1 (0.0)	5/7 (71.4)	71.4	
		95% CI	0.0; 97.5	29.0; 96.3	38.0; 100.0	0.3750
Skin type	Type I	n/N (%)	0/0 (0.0)	1/1 (100)	–	
		95% CI	–	2.5; 100.0	–	–
	Type II	n/N (%)	6/12 (50.0)	25/28 (89.3)	39.3	
		95% CI	21.1; 78.9	71.8; 97.7	8.8; 69.8	0.0122
	Type III	n/N (%)	1/19 (5.3)	19/19 (100)	94.7	
		95% CI	0.1; 26.0	82.4; 100.0	84.7; 100.0	<0.0001
Treatment area	A	n/N (%)	6/17 (35.3)	31/32 (96.9)	61.6	
		95% CI	14.2; 61.7	83.8; 99.9	38.1; 85.1	<0.0001
	B	n/N (%)	1/14 (7.1)	18/22 (81.8)	74.7	
		95% CI	0.2; 33.9	59.7; 94.8	53.7; 95.7	<0.0001
	A and B	n/N (%)	0/1 (0.0)	1/1 (100)	100.0	
		95% CI	0.0; 97.5	2.5; 100.0	100.0; 100.0	1.0000

Subgroups			Placebo	BF-200 ALA	Difference in % points to BF-200 ALA	p-value*
Number of AK lesions at baseline:	up to 5	n/N (%)	5/18 (27.8)	29/32 (90.6)	62.8	
		95% CI	9.7; 53.5	75.0; 98.0	39.8; 85.9	<0.0001
	6 or more	n/N (%)	2/14 (14.3)	21/23 (91.3)	77.0	
		95% CI	1.8; 42.8	72.0; 98.9	55.4; 98.7	<0.0001
AK lesion area	≤400 mm^2	n/N (%)	6/26 (23.1)	39/44 (88.6)	65.6	
		95% CI	9.0; 43.6	75.4; 96.2	46.8; 84.3	<0.0001
	>400 mm^2	n/N (%)	1/6 (16.7)	11/11 (100)	83.3	
		95% CI	0.4; 64.1	71.5; 100.0	53.8; 100.0	0.0010
AK history	Naïve	n/N (%)	0/2 (0.0)	8/8 (100)	100.0	
		95% CI	0.0; 84.2	63.1; 100.0	100.0; 100.0	0.0222
	Non-naive	n/N (%)	7/30 (23.3)	42/47 (89.4)	66.0	
		95% CI	9.9; 42.3	76.9; 96.5	48.5; 83.5	<0.0001

*exploratory Fisher's exact test p-value; AK= actinic keratosis; CI= confidence interval; n= number of responders; N= number of patients with available data; PDT= photodynamic therapy.

Secondary endpoints

A hierarchic test procedure was used for confirmatory hypothesis testing of secondary variables measured during the double-blind treatment period. These tests were to be performed in a strictly pre-defined order to ensure the family-wise error rate. The results of the secondary endpoints are presented in this pre- defined order.

Histopathological confirmed response rates (HCR)

Assessments of HCR rates were based on the results from the biopsy taken 12 weeks after the last PDT from a representative AK lesion selected at screening.

Table 9: Histopathological confirmed response rates 12 weeks after last PDT

	Placebo	BF-200 ALA	Difference in % points to BF-200 ALA
N with data	27	54	
Responder, n (%)	6 (22.2)	42 (77.8)	55.6
95% CI	8.6; 42.3	64.4; 88.0	36.3; 74.8
p-value Fisher's exact test			<0.0001

CI= confidence interval, Clopper-Pearson CIs; N= number of patients; n= number of responders; PDT= photodynamic therapy.
Missing investigator's assessments were replaced by the last available observation that allowed an assessment of the outcome.

The HCR was evaluated in subgroups, the HCR rates were higher in the BF-200 ALA group compared to placebo and the comparison between BF-200 ALA and placebo by Fisher's exact test yielded low p-values in most subgroups except for the subgroups with too small sample size to allow a quantitative assessment of the treatment effect (data not shown).

Patient complete response 12 weeks after PDT-1

At 12 weeks after PDT-1, patient complete response rates were considerably higher in the BF- 200 ALA group than in the placebo group (61.8% vs. 9.4%) and the difference in responder rates between the groups was statistically significant.

Table 10: Patient complete response 12 weeks after PDT-1 - FAS

	Placebo	BF-200 ALA	Difference in % points to BF-200 ALA
N with data	32	55	
Responder, n (%)	3 (9.4)	34 (61.8)	52.4
95% CI	2.0; 25.0	47.7; 74.6	36.1; 68.8
p-value Fisher's exact test			<0.0001

CI= Confidence interval, Clopper-Pearson CIs; N= number of patients n= number of responders; PDT= Photodynamic therapy.

In all subgroups, the patient complete response 12 weeks after PDT-1 were higher in the BF- 200 ALA group compared to the placebo group and the comparison between BF-200 ALA and placebo by Fisher's exact test yielded low p-values in most subgroups except for the subgroups with too small sample size to allow a quantitative assessment of the treatment effect (data not shown).

Lesion complete response 12 weeks after last PDT

The number of completely cleared individual lesions at each assessment was analysed by means of negative binomial regression with factor treatment and number of AK lesions at baseline as covariate. The results are summarized in Table 11.

Table 11: Lesion complete response 12 weeks after last PDT - FAS

	Placebo	BF-200 ALA	Difference in % points to BF-200 ALA
Number of lesions	173	298	
Cleared lesions, n (%)	57 (32.9)	281 (94.3)	61.3
95% CI	26.0; 40.5	91.0; 96.6	53.9; 68.8
p-value*			<0.0001

*Negative binominal regression; CI= Confidence interval; n= number of cleared AK lesions; PDT= Photodynamic therapy.

In all subgroups analysed, lesion complete responses 12 weeks after last PDT were higher in the BF-200 ALA group compared to the placebo group. For both treatment groups, Grade I AK lesions at baseline had higher response rate 12 weeks after the last PDT than Grade II lesions (99.1% vs. 91.7% in the BF-200 ALA group and 49.2% vs. 24.1% in the placebo group). Likewise, AK lesions located on treatment area A (face) had higher response to treatment than AK lesions located on treatment area B (bald scalp) (97.1% vs. 90.2% in the BF-200 ALA group and 47.3% vs. 16.3% in the placebo group).

Patient partial response 12 weeks after last PDT – FAS

Table 12: Patient partial response 12 weeks after last PDT - FAS

	Placebo	BF-200 ALA	Difference in % points to BF-200 ALA
N with data	32	55	
Responder, n (%)	8 (25.0)	52 (94.5)	69.5
95% CI	11.5; 43.4	84.9; 98.9	53.4; 85.7
p-value Fisher's exact test			<0.0001

CI= confidence interval, Clopper-Pearson CIs; N= number of patients; n= number of responders; PDT= photodynamic therapy.
Missing investigator's assessments were replaced by the last available observation that allowed an assessment of the outcome.

In all subgroups, patient partial response rates12 weeks after last PDT were higher in the BF- 200 ALA group compared to the placebo group.

Mean size and changes in total lesion area 12 weeks after last PDT compared to baseline– FAS

Table 13: Mean size and changes in total lesion area 12 weeks after last PDT compared to baseline - FAS

Total lesion area	Mean (SD)		p-value*
	Placebo (N=32)	BF-200 ALA (N=55)	
Size (mm^2) at screening	315.1 (91.44)	316.2 (92.93)	-
Size in (mm^2) 12 week after last PDT	163.3 (139.22)	4.8 (25.42)	<0.0001
Percentage change	–45.5 (42.96)	–98.2 (9.65)	-

*ANCOVA p-value for treatment; N= number of patients; SD= standard deviation.
Missing data were replaced by the last available observation that allowed an assessment of the outcome.

The mean percentage reduction in total lesion area per patient 12 weeks after last PDT compared to baseline was higher in the BF-200 ALA group than in the placebo group (98.2% vs. 45.5%). In all subgroups, mean percentage reductions in total lesion area per patient 12 weeks after last PDT were higher in the BF-200 ALA group than in the placebo group. The comparison between BF-200 ALA and placebo by ANCOVA yielded low p-values for most subgroups, except for the subgroups with too small sample sizes (data not shown).

Overall cosmetic outcome 12 weeks after last PDT

Table 14: Cosmetic outcome 12 weeks after last PDT - FAS

Outcome	Patients with sum score at baseline of 0 to 3		Patients with sum score at baseline of 1 to 3 (0 excluded)	
	Placebo N=29	BF-200 ALA N=54	Placebo N=26*	BF-200 ALA N=48*
Very good, n (%)	5 (17.2)	19 (35.2)	5 (19.2)	19 (39.6)
Good, n (%)	4 (13.8)	13 (24.1)	4 (15.4)	13 (27.1)
Satisfactory, n (%)	6 (20.7)	13 (24.1)	6 (23.1)	11 (22.9)
Unsatisfactory, n (%)	8 (27.6)	6 (11.1)	7 (26.9)	3 (6.3)
Impaired, n (%)	6 (20.7)	3 (5.6)	4 (15.4)	2 (4.2)
p-value[#]	-	0.0033	-	0.0032

*Number of patients with baseline sum score >0; [#]Wilcoxon-Mann-Whitney test; CI= confidence interval; N= number of patients; n= number of patients with particular cosmetic outcome.

In most of the subgroups, a higher percentage of patients had "very good or good" cosmetic outcome 12 weeks after the last PDT (with baseline sum score of 0 excluded) in the BF-200 ALA group than in placebo.

Patient complete response 3-4 weeks after PDT-1, 3-4 weeks and 12 weeks after PDT-2, and 3-4 weeks after last PDT

Overall, the complete responder rates were considerably higher in the BF-200 ALA group compared to placebo at all assessment time points.

Table 15: Patient complete response at each assessment - FAS

Time point	Placebo		BF-200 ALA	
	n/N (%)	95% CI	n/N (%)	95% CI
3-4 weeks after PDT-1	2/32 (6.3)	0.8; 20.8	29/55 (52.7)	38.3; 66.3
12 weeks after PDT-1	3/32 (9.4)	2.0; 25.0	34/55 (61.8)	47.7; 74.6
3-4 weeks after PDT-2	2/29 (6.9)	0.8; 22.8	16/21 (76.2)	52.8; 91.8
12 weeks after PDT-2	4/29 (13.8)	3.9; 31.7	16/21 (76.2)	52.8; 91.8
3-4 weeks after last PDT	3/32 (9.4)	2.0; 25.0	41/55 (74.5)	61.0; 85.3
12 weeks after last PDT	7/32 (21.9)	9.3; 40.0	50/55 (90.9)	80.0; 97.0

CI= Confidence interval; n= number of responders; N= number of patients with available data; PDT= photodynamic therapy.

Ancillary analyses

Follow-up (FU) phase of the study and the end of the FU of 12 months after last PDT

The database lock for the follow up phase was 28 May 2015. All 80 patients who completed the clinical phase (54 patients in the BF-200 ALA group and 26 patients in the placebo group) and 4 of 7 patients

withdrawn from the clinical phase (all in the placebo group) were included in the FU. Thus, 84 patients overall (54 patients in the BF-200 ALA group and 30 patients in the placebo group) entered the FU phase of the study. In the BF-200 ALA group, 49 patients were complete responders 12 weeks after the last PDT (33 patients 12 weeks after PDT1, and 16 patients 12 weeks after PDT2), in the vehicle group 7 patients were complete responders (3 patients 12 weeks after PDT1, and 4 patients 12 weeks after PDT2). 54 patients in the BF-200 ALA group and 26 patients of the vehicle group completed the FU. 4 patients (all in the vehicle group) prematurely discontinued the FU phase due to being lost to follow-up.

The related number of lesions entering FU was 294 in the BF-200 ALA group and 162 in the vehicle group. Of these lesions 247 (93.9%) were cleared after the last PDT (84.0% after PDT1 and 31.3% after PDT2) in the BF-200 ALA group. In the vehicle group, 52 (32.1%) were cleared after the last PDT (33 (20.4%) after PDT1 and 34 (21.0%) after PDT2). For 1 patient in the BF-200 ALA group (patient 0407), the assessment of one AK lesion 12 weeks after the last PDT was changed by the investigator from cleared to non-cleared after primary analysis reporting, which resulted in a slight difference in the total number of cleared lesions 12 months after last PDT between FAS and FAS-FUP analysis sets. Furthermore, 4 AK lesions were not included in the FAS-FUP as the patient with these cleared lesions at the end of the clinical phase did not enter the FU. The subject based evaluation was performed with all subjects in the follow-up period who were completely cleared at the end of the study (49 patients in the BF-200 ALA and 7 patients in the vehicle groups). In the BF-200 ALA group, recurrent AK lesions were observed in approximately 25% of those patients at 6 months FU (12 of 49 patients) and another 6 (12%) patients at 12 months FU. In the vehicle group, of 7 patients with complete remission after the last PDT, 6 (85.7%) patients remained cleared during the FU and 1 (14.3%) patient had a recurrent AK lesion at 6 months FU (Table 16).

Table 16: Patient recurrence rate of AK lesions during follow-up (FAS FU population), ALA-AK CT007 follow-up

		Vehicle		BF-200 ALA	
		n	%	n	%
End of study	Completely cleared (N)	7		49	
6-month follow-up	Completely cleared	6	85.7	37	75.5
	≥1 recurrent AK lesion since last visit	1	14.3	12	24.5
12-month follow-up	Completely cleared	6	85.7	31	63.3
	≥1 recurrent AK lesion since last visit	0	0	6	12.2
Total follow up	Completely cleared	6	85.7	31	63.3
	≥1 recurrent AK lesion	1	14.3	18	36.7

End of study: 3 months after last PDT
N: number of lesions with complete response and follow-up; n: number of lesions with event

Lesion recurrence rates were low in both treatment groups, with 1.9% and 6.2% in the vehicle and BF-200 ALA groups, respectively, at the 6-month follow-up visit. Lower lesion recurrence rates were observed after the second 6-month period of the FU (at FU2/since FU1) with 0% and 2.9%, respectively (Table 17).

Table 17: Lesion recurrence rates for all lesion-based populations (FASFU), ALA-AK-CT007

		Vehicle		BF-200 ALA	
		n	%	n	%
End of study	Cleared (N)	52		276	
6 month follow-up	Cleared	51	98.1	256	92.8
	Recurred since last visit	1	1.9	17	6.2
12 month follow-up	Cleared	51	98.1	251	90.9
	Recurred since last visit	0	0	8	2.9
Total follow up	Cleared	51	98.1	251	90.9
	Recurred	1	1.9	25	9.1

End of study: 3 months after last PDT
N: number of lesions with complete response and follow-up; n: number of lesions with event

Since field treatment was applied in the ALA-AK-CT007 study, the follow-up of the skin quality parameters (including skin surface, hyperpigmentation, hypopigmentation, mottled or irregular pigmentation, degree of scarring, and atrophy), as assessed by the investigator at FU1 and FU2 was of particular interest as the larger coherent areas outside the actual lesions allowed a better assessment of the cosmetic outcome. For the assessment, a 4-point scale (none, mild, moderate, and severe) was applied. All parameters of skin quality were further improved compared to the end of the study. At both FU visits, improvements were reported for a higher proportion of patients in the BF-200 ALA group compared to the vehicle group. Skin parameters improved continuously between FU1 and FU2 (Table 18).

Table 18: Frequency of skin quality changes at baseline and 6 and 12 months after last PDT by severity, ALA-AK-CT007 (ALA-AK-CT007 follow up; FASFU)

		Placebo			AMELUZ®		
		Baseline	6 months	12 months	Baseline	6 months	12 months
Roughness/ dryness/ scaliness	None	3 (11.1)	15 (55.6)	15 (57.7)	8 (14.8)	34 (63.0)	39 (72.2)
	Mild	15 (55.6)#	9 (33.3)	9 (34.6)	27 (50.0)	15 (27.8)	14 (25.9)
	Moderate	9 (33.3)	3 (11.1)	2 (7.7)	19 (35.2)	4 (7.4)	1 (1.9)
	Severe	0 (–)	0 (–)	0 (–)	0 (–)	1 (1.9)	0 (–)
Hyper-pigmentation	None	8 (29.6)#	13 (48.1)	16 (61.5)	22 (40.7)	35 (64.8)	41 (75.9)
	Mild	16 (59.3)	10 (37.0)	9 (34.6)	28 (51.9)	16 (29.6)	13 (24.1)
	Moderate	3 (11.1)	4 (14.8)	1 (3.8)	4 (7.4)	3 (5.6)	0 (–)
	Severe	0 (–)	0 (–)	0 (–)	0 (–)	0 (–)	0 (–)
Hypo-pigmentation	None	14 (51.9)#	15 (55.6)	18 (69.2)	29 (53.7)	42 (77.8)	48 (88.9)
	Mild	12 (44.4)	9 (33.3)	7 (26.9)	23 (42.6)	10 (18.5)	6 (11.1)
	Moderate	1 (3.7)	3 (11.1)	1 (3.8)	2 (3.7)	2 (3.7)	0 (–)
	Severe	0 (–)	0 (–)	0 (–)	0 (–)	0 (–)	0 (–)
Mottled or irregular pigmentation	None	13 (48.1)#	14 (51.9)	19 (73.1)	28 (51.9)	37 (68.5)	44 (81.5)
	Mild	11 (40.7)	9 (33.3)	4 (15.4)	24 (44.4)	13 (24.1)	9 (16.7)
	Moderate	3 (11.1)	4 (14.8)	3 (11.5)	2 (3.7)	4 (7.4)	1 (1.9)
	Severe	0 (–)	0 (–)	0 (–)	0 (–)	0 (–)	0 (–)
Degree of scarring	None	20 (74.1)#	20 (74.1)	23 (88.5)	40 (74.1)	44 (81.5)	50 (92.6)
	Mild	6 (22.2)	5 (18.5)	3 (11.5)	12 (22.2)	8 (14.8)	4 (7.4)
	Moderate	1 (3.7)	2 (7.4)	0 (–)	2 (3.7)	2 (3.7)	0 (–)
	Severe	0 (–)	0 (–)	0 (–)	0 (–)	0 (–)	0 (–)
Atrophy	None	19 (70.4)#	21 (77.8)	24 (92.3)	37 (68.5)	48 (88.9)	52 (96.3)
	Mild	8 (29.6)	4 (14.8)	2 (7.7)	16 (29.6)	4 (7.4)	2 (3.7)
	Moderate	0 (–)	2 (7.4)	0 (–)	1 (1.9)	2 (3.7)	0 (–)
	Severe	0 (–)	0 (–)	0 (–)	0 (–)	0 (–)	0 (–)

*Baseline data for patients who had FU1 are presented for all skin quality parameters; for those marked with "#" data were collected from 1 patient less at FU2 compared to FU1. Percentages are based on number of patients with data.

Summary of main study

A summary of the efficacy results from the main study supporting the present application is presented below. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

ALA-AK-CT007

Multicenter, randomized, double-blind, placebo-controlled, parallel group (2:1 ratio). 84 patients were planned to be randomized.

Primary objective: Comparison of efficacy of BF-200 ALA with placebo for field-directed treatment of mild to moderate actinic keratosis (AK) with PDT, using BF-RhodoLED lamp.
Secondary objectives: Evaluation of safety and secondary efficacy parameters related to BF-200 ALA for field-directed treatment of AK with PDT, using BF-RhodoLED lamp.
Efficacy results: Overall complete responder rates 12 weeks after the last PDT considerably higher in the BF-200 ALA group (50 [90.9%] patients) than in the placebo group (7 [21.9%] patients). The results of the Fisher's exact test of the comparison in complete responder rates between BF- 200 ALA

and placebo (p<0.0001) demonstrated the superiority of BF-200 ALA to placebo. The robustness of these results was confirmed by the per-protocol (PP) analysis.
The confirmatory analysis of all key secondary variables supported the superiority of BF-200 ALA to placebo shown in the primary analysis. The results demonstrated a significant treatment effect of BF-200 ALA to placebo for all key secondary efficacy variables tested in the hierarchic multiple test procedure.
Superiority of BF-200-ALA to placebo was also supported by the exploratory analyses of the complete and partial responder rates, lesion complete response, and change from baseline in total lesion area at all assessment time points. No patients in the BF-200 ALA group had new AK lesions. In the placebo group, only one patient presented with new lesions 12 weeks after PDT-2. All parameters of skin quality (skin surface, hyperpigmentation, mottled or irregular pigmentation, degree of scarring, and atrophy) improved in higher proportions of patients in the BF-200 ALA group compared to the placebo group 12 weeks after the last PDT. The proportion of patients with improvements in skin quality due to treatment with BF-200 ALA ranged from 35.7% to 69.6% of patients (excluding baseline evaluation "none") for improvement in degree of scarring and skin surface, respectively. Very good or good cosmetic outcome was reported for 32 (66.7%) patients in the BF-200 ALA group and 9 (34.5%) patients in the placebo group.
All efficacy variables in this study were analyzed in an exploratory way for a number of subgroups including: (maximum) baseline severity of AK lesions, age, gender, skin type and skin type group, treatment area, number of AK lesions at baseline, AK history, and study center. For all subgroups, the results of the efficacy variables at all assessment time points supported the superiority of BF-200 ALA over placebo shown in the overall population. Patients with Grade I AK lesions at baseline had higher complete responder rates 12 weeks after the last PDT than patients with Grade II lesions for both treatment groups (10 [100%] vs. 40 [88.9%] patients in the BF-200 ALA group and 5 [71.4%] vs. 2 [8.0%] patients in the placebo group). Results for the treatment area subgroups revealed
higher overall responder rates in patients with AK lesions located on the face only (treatment area A) than in patients with AK lesions located on the bald scalp only (treatment area B) (96.9% vs. 81.8% in the BF-200 ALA group and 35.3% vs. 7.1% in the placebo group). The vast majority of patients in the BF-200 ALA group were satisfied by the treatment: 49 (90.7%) patients rated their satisfaction as "very good or good" and only 1 (1.9%) patient was not satisfied by the treatment. In the placebo group, "very good or good" satisfaction was reported by 13 (44.8%) patients and more than one third (11 [37.9%] patients) were unsatisfied by the treatment. None of the patients was impaired by the BF-200 ALA or placebo treatments.

Supportive studies

<u>ALA-AK-CT002- 12 month follow up</u>
The full description of the study was presented in the EPAR for the initial marketing authorisation. Of the 570 subjects in the ITT population, 549 completed the clinical treatment phase of the study and entered the follow-up phase (ITTFU population): 68, 241 and 240 from the vehicle, BF-200 ALA and Metvix groups, respectively. Of the 549 patients in the ITTFU, follow-up was completed by 532 (96.9%) patients.

Outcomes and estimation
Recurrence at the 6- or 12-month follow-up (combined) in complete responders who completed follow-up was observed for 3 (23.1%) patients who had received vehicle and 77 (41.6%) and 69 (44.8%) patients who had received BF-200 ALA and Metvix, respectively. At the end of follow-up (12 months after the last PDT) 10 (79.9%) patients in the vehicle groups, 108 (58.4%) patients in the BF-200 ALA group and 85 (55.2%) patients in the Metvix group had still no recurrent lesions.

Table 19: Patient recurrence rate of AK lesions during follow-up (ITTFU population), ALA-AKCT002

		Vehicle		BF-200 ALA		Metvix®	
		n/N	%	n/N	%	n/N	%
6 month follow-up	Recurrence	2/13	15.4	36/188	19.1	28/154	18.2
12 month follow-up	Recurrence	1/13	7.7	41/185	22.2	41/154	26.6
Total follow-up	Recurrence	3/13	23.1	77/185	41.6	69/154	44.8

Source: CSR ALA-AK-CT002 Addendum I, 11.2.1.1
N: number of patients who had complete responder with follow-up; n: number of patients with event

Patient recurrence rates by type of lamp used during PDT were slightly in favor for narrow spectrum lamps.

Table 20: Patient recurrence rate of AK lesions during follow-up by type of lamp (ITT FU population), ALA-AK-CT002 follow up

		Vehicle		BF-200 ALA		Metvix®	
		n/N	%	n/N	%	n/N	%
6-month follow-up	Narrow spectrum	1/5	20.0	14/101	13.9	11/81	13.6
	Broad spectrum	1/8	12.5	22/87	25.3	17/73	23.3
12-month follow-up	Narrow spectrum	1/5	20.0	25/98	25.5	22/81	27.2
	Broad spectrum	0/8	0	16/87	18.4	19/73	26.0
Total follow-up	Narrow spectrum	2/5	40.0	39/98	39.8	33/81	40.7
	Broad spectrum	1/8	12.5	38/87	43.7	36/78	49.3

Source: CSR ALA-AK-CT002 Addendum I, Table 11.2.1.4
N: number of patients who had complete responder with follow-up; n: number of patients with event

The AK recurrence rate was also calculated on a lesion basis. The AK lesion recurrence rate was 3.6%, 11.4% and 6.6% in the vehicle, BF-200 ALA and Metvix groups, respectively, at the 6-month follow-up visit, and 13.1%, 14.7% and 18.8%, respectively, at the 12-month follow up visit.

Table 21: Lesion recurrence rate of AK lesions during follow-up (ITT FU population), ALA-AKCT002 follow-up

		Vehicle		BF-200 ALA		Metvix®	
		n/N	%	n/N	%	n/N	%
6 month follow-up	Recurrence	3/84	3.6	79/1043	7.0	62/873	6.6
12 month follow-up	Recurrence	8/70	11.4	127/862	14.7	140/743	18.8
Total follow-up	Recurrence	11/84	13.1	206/1043	19.8	202/873	23.1

Source: CSR ALA-AK-CT002 Addendum I, 11.2.2.1
N: number of lesions which were totally cleared with follow-up; n: number of lesions with event

ALA-AK-CT003 - 12 month follow up

The full description of the study was presented in the EPAR for the initial marketing authorisation. 122 subjects (81 subjects receiving BF-200 ALA and 41 subjects receiving placebo) entered the main phase of the study. 8 subjects (4 in each treatment group) did not complete the main phase as planned and did not enter the follow up phase, i.e. 77 subjects in the BF-200 ALA and 37 subjects in the placebo group entered the follow-up phase. 4 subjects (2 in each treatment group) were lost to follow-up prior to any follow-up assessments. Month 6 assessments were available for 72 subjects in the BF-200 ALA

and 34 subjects in the placebo group, month-12 assessments were available for 71 subjects in the BF-200 ALA and 32 subjects in the placebo group.

Of the 114 subjects in the ITT population, all 114 completed the clinical treatment phase of the study, and 102 patients completed both the 6-month and 12-month follow-up: 70 in the BF-200 ALA group and 32 in the vehicle group. The subject based evaluation was performed with all subjects in the follow-up period who were completely cleared at the end of the study (53 patients in the BF-200 ALA and 5 patients in the vehicle groups).

Outcomes and estimation

Patient AK recurrence rates were 17.0% and 40.0% for the BF-200 ALA and vehicle groups, respectively, at the 6-month follow-up visit, and 11.3% and 0%, respectively at the 12-month follow-up visit. Patient recurrence rates were in favor for narrow spectrum lamps with 11.1% at the 6-month and 12 months follow-up visit each versus 23.1% and 11.5%, respectively for broad spectrum lamps.

Table 22: Patient recurrence rate of AK lesions during follow-up (FASFU population), ALA-AK-CT003 follow-up

		Vehicle		BF-200 ALA	
		n	%	n	%
End of study	Completely cleared	5		53	
6-month follow-up	Completely cleared	2	40	42	79.2
	≥1 recurrent AK lesion since last visit	2	40	9	17.0
	Lost to follow-up since last visit	1	20	2	3.8
12-month follow-up	Completely cleared	2	40	34	64.2
	≥1 recurrent AK lesion since last visit	0	0	6	11.3
	Lost to follow-up since last visit	0	0	2	3.8
Total follow up	Completely cleared	2	40	34	64.2
	≥1 recurrent AK lesion	2	40	15	28.3
	Lost to follow-up	1	20	4	7.5

End of study: 3 months after last PDT
N: number of patients who had complete responder with follow-up; n: number of patients with event

Table 23: Patient AK recurrence rates during follow-up by type of lamp (FASFU population), ALAAK-CT003 follow-up

		Narrow spectrum				Broad spectrum			
		Vehicle		BF-200 ALA		Vehicle		BF-200 ALA	
		n	%	n	%	n	%	n	%
End of study	Cleared	2		27		3		26	
6 month follow-up	Cleared	2	100	24	88.9	0	0	18	69.2
	Recurred since last visit	0	0	3	11.1	2	66.7	6	23.1
	Lost to follow-up	0	0	0	0	1	33.3	2	7.7
12 month follow-up	Cleared	2	100	20	74.1	0	0	14	53.8
	Recurred since last visit	0	0	3	11.1	0	0	3	11.5
	Lost to follow-up	0	0	1	3.7	0	0	1	3.8
Total follow up	Completely cleared	2	100	20	74.1	0	0	14	53.8
	≥1 recurrent AK lesion	0	0	6	22.2	2	66.7	9	34.6
	Lost to follow-up	0	0	1	3.7	1	33.3	3	11.5

End of study: 3 months after last PDT
N: number of patients who had complete responder with follow-up; n: number of patients with event

The AK recurrence rate was also calculated on a lesion basis. The AK lesion recurrence rate was 4.4% and 7.1% in the vehicle and BF-200 ALA groups, respectively, at the 6-month follow-up visit, and 4.4% and 7.9%, respectively, at the 12 -month follow-up visit. Again, recurrence rates were lower for narrow spectrum lamps compared to lesions treated with broad spectrum lamps.

Table 24: AK lesion recurrence rate during follow-up (FASFU population), ALA-AK-CT003 follow-up

		Vehicle		BF-200 ALA	
		n	%	n	%
End of study	Cleared	45		353	
6 month follow-up	Cleared	31	68.9	312	88.4
	Recurred since last visit	2	4.4	25	7.1
	Lost to follow-up	12	26.7	16	4.5
12 month follow-up	Cleared	29	64.4	274	77.6
	Recurred since last visit	2	4.4	29	7.9
	Lost to follow-up	0	0	10	2.8
Total follow up	Cleared	29	64.4	274	77.6
	Recurred	4	8.8	54	15.0
	Lost to follow-up	12	26.7	26	7.3

End of study: 3 months after last PDT
N: number of lesions with complete response and follow-up; n: number of lesions with event

Table 25: AK lesion recurrence rate during follow-up by type of lamp (FASFU population), ALA-AK-CT003 follow-up

		Narrow spectrum				Broad spectrum			
		Vehicle		BF-200 ALA 10%		Vehicle		BF-200 ALA 10%	
		n	%	n	%	n	%	n	%
End of study	Cleared	12		164		33		189	
6 month follow-up	Cleared	12	100	161	98.2	19	57.6	151	79.9
	Recurred since last visit	0	0	3	1.8	2	6.1	22	11.6
	Lost to follow-up	0	0	0	0	12	36.4	16	8.5
12 month follow-up	Cleared	12	100	148	90.2	17	51.5	126	66.7
	Recurred since last visit	0	0	8	4.9	2	6.1	20	10.6
	Lost to follow-up	0	0	5	3.0	0	0	5	2.6
Total follow up	Cleared	12	100	148	90.2	17	51.5	126	66.7
	Recurred	0	0	11	6.7	4	12.2	42	22.1
	Lost to follow-up	0	0	5	3.0	12	36.4	21	11.1

End of study: 3 months after last PDT

N: number of lesions with complete response and follow-up; n: number of lesions with event

Analysis performed across trials (pooled analyses and meta-analysis)

A pooled analysis was performed with efficacy data from the three Phase III studies ALA-AK-CT002, ALA-AK-CT003, and ALA-AK-CT007.

Table 26: Studies included in the integrated summary of efficacy

Study Number	Study Design	Treatment Regimen	Primary Efficacy Endpoint	Primary Analysis Set	Statistical Methods
ALA-AK-CT007 (Germany)	Phase III, randomized, double-blind, placebo-(vehicle-) controlled, parallel-group (2:1 ratio) study.	Up to two PDTs separated by 12 weeks. One to two fields of 4 to 8 mild to moderate AK lesions were treated for a total area of about 20 cm^2 ("field-directed treatment"). - BF-200 ALA - Placebo/ vehicle	Complete clearance rate, defined as percentage of patients for whom all treated AK lesions were completely cleared 12 weeks after the last PDT.	FAS, defined as all patients randomized and treated at least once with the IMP after randomization .	Fisher's exact test was used to test superiority of BF-200 ALA over placebo at a significance level of 0.05 (two-sided).
ALA-AK-CT003 (Germany)	Phase III, randomized, double-blind, placebo-(vehicle-) controlled, parallel group (2:1 ratio) study.	Up to two PDTs separated by 12 weeks. For each PDT up to 4 to 8 distinct mild to moderate AK lesions were treated with IMP with a diameter of 0.5 to 1.5 cm (up to a total area of 20 cm^2). - BF-200 ALA - Placebo/ vehicle	Complete clearance rate, defined as percentage of patients for whom all treated AK lesions were completely cleared 12 weeks after the last PDT.	FAS, which included all subjects who received treatment and had at least one post-dose assessment for the primary variable.	CMH test, accounting for centers as stratifying variable, was used to test treatment effect. The test was a two-sided test at an alpha-level of 0.05.
ALA-AK-CT002 (Germany, Austria, Switzerland)	Phase III, randomized, reference therapy controlled and placebo-(vehicle-) controlled, observer blind to reference therapy and double blind to placebo, parallel-group study.	Up to two PDTs separated by 12 weeks. Treatment with IMP of 4 to 8 distinct mild to moderate AK lesions. The total lesion area was not to exceed 20 cm^2. An occlusive dressing was applied, which was removed after 3 hours, followed by PDT. - BF-200 ALA - Placebo / vehicle - MAL cream.	Complete clearance rate, defined as percentage of patients for whom all treated AK lesions were completely cleared 12 weeks after the last PDT.	ITT, defined as all subjects randomized and treated at least once with IMP after randomization .	Hierarchical procedure. Step 1: BF-200 ALA superior to placebo using a chi-square test with a two-sided alpha of 0.05. Step 2: BF-200 ALA non-inferior to MAL cream applying a non-inferiority margin of $\Delta = 15\%$.

The primary endpoint for all three studies was the rate of complete clearance, defined as the percentage of patients for whom all treated AK lesions were completely cleared 12 weeks after the last PDT.

An overview of the primary efficacy results is shown below.

Table 27: Rate of patient complete response 12 weeks after last PDT - FAS

		Vehicle (N= 148)			BF-200 ALA (N=383)			Difference [95% CI]	P value [a]
		N	n	%	N	n	%		
Step I [b]	Overall	148	25	16.9	383	297	77.5	60.7 (53.3, 68.0)	<0.0001
Step II [b]	All narrow spectrum lamps, pooled [c]	86	14	16.3	211	183	86.7	70.5 (61.4, 79.5)	<0.0001
Step III [b]	All broad spectrum lamps, pooled [c]	62	11	17.7	172	114	66.3	48.5 (36.7, 60.4)	<0.0001
Step IV [b]	Narrow spectrum, by type of lamp								
	BF-RhodoLED	32	7	21.9	53	48	90.6	68.7 (52.3, 85.0)	<0.0001
	Aktilite	43	4	9.3	122	102	83.6	74.3 (63.4, 85.2)	<0.0001
	Omnilux	11	3	27.3	35	32	91.4	64.2 (36.3, 92.1)	<0.0001

n (%): number (%) of patients; %: percent of patients

[a] Fisher's exact test

[b] The tests were done in a hierarchical manner, proceeding with Step II, only after the difference at Step I showed statistical significance; with Step III, only after the treatment difference at Step II showed statistical significance; with Step IV, only after the treatment difference at Step III showed statistical significance.

[c] If the lamp type was changed within a patient from PDT1 to PDT2, the patient was excluded from the subgroup analyses on lamp type for complete response.

Secondary endpoints

- Rate of patient complete response by PDT session and type of lamp

Table 28: Rate of patient complete response by PDT session, visit and type of lamp

		Vehicle (N= 148)			BF-200 ALA (N=383)			Difference [95% CI]	P value [a]
		N	n	%	N	n	%		
Overall									
PDT1	Week 4	148	6	4.1	383	144	37.6	33.5 [27.7, 39.3]	<0.0001
	Week 12		10	6.8		192	50.1	43.4 [36.9, 49.8]	<0.0001
PDT2	Week 4	138	14	10.1	191	99	51.8	41.7 [33.0, 50.4]	<0.0001
	Week 12		15	10.9		105	55.0	44.1 [35.3, 52.9]	<0.0001
Last PDT	Week 4	148	18	12.2	383	220	57.4	45.3 [38.1, 52.5]	<0.0001
	Week 12		25	16.9		297	77.5	60.7 [53.3, 68.0]	<0.0001
Narrow spectrum lamps									
PDT1	Week 4	86	4	4.7	211	95	45.0	40.4 [32.3, 48.4]	<0.0001
	Week 12		5	5.8		123	58.3	52.5 [44.2, 60.8]	<0.0001
PDT2	Week 4	81	6	7.4	88	57	64.8	57.4 [45.9, 68.9]	<0.0001
	Week 12		9	11.1		60	68.2	57.1 [45.2, 69.0]	<0.0001
Last PDT	Week 4	86	8	9.3	211	140	66.4	57.0 [48.2, 65.9]	<0.0001
	Week 12		14	16.3		183	86.7	70.5 [61.4, 79.5]	<0.0001
Broad spectrum lamps									
PDT1	Week 4	62	2	3.2	172	49	28.5	25.3 [17.2, 33.3]	<0.0001
	Week 12		5	8.1		69	40.1	32.1 [22.1, 42.0]	<0.0001
PDT2	Week 4	57	8	14.0	103	42	40.8	26.7 [13.7, 39.8]	0.0006
	Week 12		6	10.5		45	43.7	33.2 [20.7, 45.6]	<0.0001
Last PDT	Week 4	62	10	16.1	172	80	46.5	30.4 [18.6, 42.2]	<0.0001
	Week 12		11	17.7		114	66.3	48.5 [36.7, 60.4]	<0.0001

- Rate of lesion complete response by PDT session and type of lamp

Table 29: Rate of lesion complete response by PDT session, visit and type of lamp

Table 28: Rate of lesion complete response by PDT session, visit and type of lamp, ISE, FAS

		Vehicle			BF-200 ALA		
		N	n	%	N	n	%
Overall							
PDT1	Week 4	883	114	12.9	2255	1446	64.1
	Week 12		201	22.8		1675	74.3
PDT2	Week 4	682	83	12.2	577	343	59.4
	Week 12		112	16.4	582	368	63.2
After last PDT	Week 4	883	237	26.8	2249	1775	78.9
	Week 12		285	32.3	2257	2009	89.0
Narrow spectrum lamps							
PDT1	Week 4	527	64	12.1	1316	950	72.2
	Week 12		92	17.5	1314	1057	80.4
PDT2	Week 4	435	45	10.3	254	178	70.1
	Week 12		74	17.0	259	186	71.8
After last PDT	Week 4	527	117	22.2	1308	1109	84.8

		Vehicle			BF-200 ALA		
		N	n	%	N	n	%
	Week 12		157	29.8	1316	1239	94.1
Broad spectrum lamps							
PDT1	Week 4	356	50	14.0	939	496	52.8
	Week 12		109	30.6	941	618	65.7
PDT2	Week 4	247	38	15.4	323	165	51.1
	Week 12		38	15.4		182	56.3
After last PDT	Week 4	356	120	33.7	941	666	70.8
	Week 12		128	36.0		770	81.8

- Change in skin quality between baseline and 12 weeks after the last PDT

Table 30: Improvement in skin quality assessment compared to baseline assessed 12 weeks after the last PDT

	Overall				Narrow spectrum lamps			
	Vehicle (N=148)		BF-200ALA (N=383)		Vehicle (N=86)		BF-200ALA (N=211)	
	n	%	n	%	n	%	n	%
Skin surface (roughness/dryness/scaliness)	26	19.0	131	34.8	16	20.5	71	34.5
Hyperpigmentation	18	13.1	64	17.0	9	11.5	36	17.5
Hypopigmentation	10	7.3	32	8.5	5	6.4	23	11.2
Mottled or irregular pigmentation	20	14.6	45	12.0	13	16.7	28	13.6
Scarring	6	4.4	19	5.1	3	3.8	10	4.9
Atrophy	4	2.9	22	5.9	1	1.3	14	6.8

For the skin quality score, skin surface (roughness/dryness/scaliness), hyperpigmentation, hypopigmentation, mottled or irregular pigmentation, degree of scarring and atrophy were each rated on a scale of 0 to 3 and the results summed for a maximum score of 18.

[a] Fisher's exact test

- Rate of patient complete response 12 weeks after last PDT by demographic factors

Table 31: Rate of patient complete response 12 weeks after last PDT by baseline disease characteristics - FAS

		Vehicle (N= 148)			BF-200 ALA (N=383)			Difference [95% CI]	P value [a]
		N	n	%	N	n	%		
Gender	Male	120	24	20.0	336	256	76.2	56.2 [47.7, 64.7]	<0.0001
	Female	28	1	3.6	47	41	87.2	83.7 [71.9, 95.4]	<0.0001
Age	≥18 to <65 years	18	3	16.7	66	56	84.8	68.2 [48.9, 87.4]	<0.0001
	≥65 to <75 years	90	18	20.0	210	160	76.2	56.2 [46.1, 66.3]	<0.0001
	≥75 years	40	4	10.0	107	81	75.7	65.7 [53.4, 78.0]	<0.0001

[a] Fisher's exact test

- Rate of patient complete response 12 weeks after last PDT by baseline characteristics

Table 32: Rate of patient complete response 12 weeks after last PDT by baseline disease characteristics - FAS

		Vehicle (N= 148)			BF-200 ALA (N=383)			Difference [95% CI]	P value [a]
		N	n	%	N	n	%		
Target skin region	Face, forehead	81	12	14.8	230	188	81.7	66.9 [57.7, 76.1]	<0.0001
	Bald scalp	46	9	19.6	111	78	70.3	50.7 [36.4, 65.0]	<0.0001
	Both	21	4	19.0	42	31	73.8	54.8 [33.3, 76.2]	<0.0001
Fitzpatrick skin type Grade	I to III	143	24	16.8	337	261	77.4	60.7 [53.1, 68.2]	<0.0001
	IV to VI	5	1	20.0	46	36	78.3	58.3 [21.2, 95.3]	0.0166
AK severity (Olsen [b])	mild	32	10	31.3	69	59	85.5	54.3 [36.2, 72.3]	<0.0001
	moderate	116	15	12.9	314	238	75.8	62.9 [55.1, 70.6]	<0.0001
Previous treatment	No	37	5	13.5	123	99	80.5	67.0 [53.9, 80.0]	<0.0001
	Non-surgical	64	10	15.6	141	105	74.5	58.8 [47.4, 70.3]	<0.0001
	Surgical	9	0	0.0	37	30	81.1	81.1 [68.5, 93.7]	<0.0001
	Both	38	10	26.3	82	63	76.8	50.5 [33.8, 67.2]	<0.0001
Size of lesion	≤ 400 mm^2	86	16	18.6	178	143	80.3	61.7 [51.6, 71.8]	<0.0001
	> 400 mm^2	62	9	14.5	205	154	75.1	60.6 [50.0, 71.2]	<0.0001
No. target lesions	≤ 5	57	10	17.5	183	150	82.0	64.4 [53.1, 75.8]	<0.0001
	≥ 6	91	15	16.5	200	147	73.5	57.0 [47.2, 66.8]	<0.0001

[a] Fisher's exact test

[b] Grade 1 or grade 2 or grade 3 according to Olsen et al. Dermatol 1991; 24: 738-743 (allocation according to maximal baseline severity)

2.4.2. Discussion on clinical efficacy

The clinical assessment for this variation application is based on the new phase III study ALA-AK-CT007 and the data on the 6 and 12 month follow up data from studies ALA-AK-CT002 and ALA-AK-CT003, which were the pivotal trials for the initial marketing authorisation application.

Design and conduct of clinical studies

The primary endpoint and the response endpoints among the set of secondary endpoints were analysed using a Fisher exact test. This was presumably specified due to low expected response rates in the placebo arm. Although in retrospect it would not have been obligatory to use an exact test, this

analysis method is considered acceptable and from a regulatory perspective, generally more conservative than the methods used in the other phase III studies of the program (a Cochran-Mantel-Haenszel test in ALA-AK-CT003 and a chi-square test in ALA-AK-CT002). Type I error control is appropriate and the hierarchical procedure for the secondary endpoints allows confirmatory conclusions also for the secondary endpoints. Therefore, the statistical methods used for analysis in study ALA-AK-CT007 were considered appropriate.

There was no considerable impact of missing data on the study results, as only 2 patients in the placebo arm and one patient in the active arm had missing observations at 12 weeks. Therefore, sensitivity analyses are not considered necessary.

The pre-specified subgroups analyses were considered appropriate. It is noted that numbers in several subgroups (Grade I AK lesions, age <= 65 years, females, skin type I, skin type IV and higher, AK lesion of <=400 mm2, AK naïve patients) were very small. Therefore, the results comparing these subgroups have to be interpreted with caution. This also relates to apparent differences in treatment effects. Overall the subgroups results can be considered consistent.

The methods used for the pooled analyses across trials of the phase III program, including the studies ALA-AK-CT007, ALA-AK-CT003 and ALA-AK-CT002, are considered appropriate. The study characteristics and key design features are considered sufficiently similar to allow a pooled analysis across the study program. The studies had the same main inclusion criteria for patients (4 to 8 AK target lesions 0.5 to 1.5 cm diameter of mild to moderate severity with an overall size of approximately 20 cm^2). In ALA-AK-CT007, the lesions were to be located within one to two fields of 20 cm^2, which was not required for the other two studies. The studies had an identical schedule for the PDT treatments and timing for the assessment of the primary efficacy endpoint and used the same primary efficacy endpoint (complete patient-based clearance rate) at 12 weeks after the last PDT.

Of note, the studies used different analysis set definitions for assessment of efficacy. The primary analysis set for efficacy of the integrated analysis comprised all patients randomised and treated at least once, and the same definition was used in studies ALA-AK-CT007 and ALA-AK-CT002, whereas in study ALA-AK-CT003, the primary analysis was performed in all patients randomized and treated at least once with the product and who had a least one post-dose assessment. Therefore, some of the results of the pooled analysis differ from the results in the original study report. However, these small differences have no impact on conclusions from the results.

Red-light illumination was chosen since light with longer wave lengths penetrates deeper into the tissue.

Efficacy data and additional analyses

For trial ALA-AK-CT007, the topical application of BF-200 ALA with PDT was shown to be superior to placebo for treatment of AK. The overall patient complete response rate 12 weeks after the last PDT was considerably higher in the BF-200 ALA group than in the placebo group (90.9% vs. 21.9% of patients, <0.0001; FAS). Results of the confirmatory analyses of all secondary efficacy variables also showed superiority of BF-200 ALA to placebo.

A higher number of patients with Grade I AK lesions at baseline were complete responders 12 weeks after the last PDT compared to patients with Grade II lesions (100% vs. 88.9% of patients treated with BF-200 ALA). Complete responder rates were higher in patients with AK lesions located on the face (treatment area A) only than in patients with AK lesions located on the bald scalp only (96.9% vs. 81.8% of patients) (treatment area B).

Topical application of BF-200 ALA resulted in improvements of skin quality 12 weeks after the last PDT compared to baseline. The most prominent improvements were observed in the skin surface

(roughness, dryness, and scaliness), reported in 69.6% of patients in the BF-200 ALA group, and mottled and irregular pigmentation, reported in 50.0% of the patients. The cosmetic outcome (with baseline sum score 0 excluded) assessed 12 weeks after the last PDT was considered as very good or good in 66.7% of patients in the BF 200 ALA group, compared to 34.6% of patients in the placebo group. The vast majority of patients treated with BF-200 ALA were satisfied by treatment results. In total, 90.7% of the patients rated their satisfaction as "very good or good" and only 1 (1.9%) patient was not satisfied by the treatment.

The follow up period for trial ALA-AK-CT007 showed that patient lesion recurrence rates were in favour for the vehicle where new lesions in the treated field(s) were observed in 4 patients (7.4%) (one lesion in one subject at month 6, and in 3 subjects at months 12) in the BF-200 ALA group compared to no new lesions were observed in the vehicle group. The MAH clarified that none of the lesions were in the treated field (the region actually treated with BF-200 ALA) and only 3 lesions (one Bowen's, one BCC, one SCC) were in the respective treatment area (either face/forehead or scalp). The placebo had one lesion about 2-fold smaller, providing evidence that there was no increased non-melanoma malignancy in the treated areas. The majority of patients in both treatment groups had at least good cosmetic outcome at the end of the FU (83.3% and 87.5% of patients in the BF-200 ALA and placebo groups, respectively). Patients' contentment was reported by a higher proportion of patients in the BF-200 ALA group than in the placebo group at the end of the FU (77.8% vs. 69.2% patients) (see clinical safety section).

Study ALA-AK-CT002 follow up data showed that patients with completely cleared lesions 12 weeks after the last PDT (i.e. at the end of the clinical treatment phase), 41.6% in the BF-200 ALA group had recurrent lesions at 6 and/or 12 months follow up compared to 44.8% in the Metvix group and 23.1% in the placebo group. Overall, cosmetic outcome was comparable for Metvix and BF-200 ALA and better than for placebo. At 12 months follow-up in subjects that had been classified as complete responders at 12 weeks after the last PDT and that were still cleared (free of lesions) after 6 months follow-up in the BF-200 ALA group, 14.7% of the lesions were reported to be recurrent, compared to 18.8% in the Metvix group and 11.4% in the placebo group. The MAH provided a retrospective analysis of the neoplasia that occurred in patients either during the clinical phase (CSR) or the follow-up (FUP) which showed that 4.9 % of the patients in the BF-200 ALA group, 9.8 % of the Metvix patients and 9.7 % of the placebo patients displayed neoplastic lesions. Therefore, there appears that there is no solid evidence that patients in the BF-200 ALA group had an increased risk of developing novo skin neoplasia (see clinical safety section).

Study ALA-AK-CT003 follow up data showed that patients with complete clearance at the end of the study, 28.3% of the subjects in the BF-200 ALA group compared to 40.0% of subjects in the placebo group had recurrent lesions during the 12-month follow-up. Comparison of the recurrence rate after BF-200 ALA treatment to placebo treatment was limited by to the low number of subjects with complete clearance (4 available subjects) and the low number of cleared lesions (45 lesions) at the end of the study in the placebo group. New AK lesions in the target area were observed slightly more often in the BF-200 ALA group than in the placebo group, however the difference was not statistically significant. Skin quality assessments and overall cosmetic outcome showed no substantial differences between the treatment groups. During a 12-month follow-up period, 15% of the lesions cleared at the end of the study after treatment with PDT and BF-200 ALA group were recurrent; in the placebo group slightly fewer lesions (8.8%) were recurrent. The MAH provided a retrospective analysis of the neoplasia that occurred in patients either during the clinical phase (CSR) or the follow-up (FUP). Indicated are the patient number and the preferred term (PT) which showed that neoplasia was detected in 3.1% in the BF-200 ALA group and 5.1% in the placebo group, indicating that there is no increased risk of novo skin neoplasia (see clinical safety section).

2.4.3. Conclusions on the clinical efficacy

Trial ALA-AK-CT007 met it's primary endpoint and showed efficacy in the treatment of field cancerisation with ALA, where overall patient complete response at 12 weeks and clearance of lesions was observed. The primary efficacy results were supported by the secondary endpoints. The results are considered statistically significant and clinically meaningful. It also showed that field-directed treatment skin quality improved continuously from baseline to FU2. Overall, the results of the FU analyses were in agreement with the data of the clinical phase by demonstrating higher rates of patient- and lesion-wise clearance in the BF-200 ALA group vs. placebo at the end of FU. Follow up data from studies ALA-AK-CT002, ALA-AK-CT003 and ALA-AKCT007 indicated that the efficacy achieved 12 weeks after the last PDT was generally maintained during a 12-month follow up period.

All Phase III studies demonstrated that the use of illumination sources with a narrow wavelength spectrum, such as the BF-RhodoLED, seems to yield higher AK clearance rates than sources with a broad wavelength spectrum. Irrespective of the lamp, BF-200 ALA showed efficacy superior to placebo.

2.5. Clinical safety

Introduction

The MAH provided a follow up for the safety results of the studies ALA-AK-CT002, ALA-AK-CT003, and ALA-AK-CT007.

Patient exposure

The number of patients exposed to PDT-1 and PDT-2 by treatment area is presented in Table 33. All 87 patients in the SAF were exposed to PDT in the first session: 32 patients received placebo and 55 patients received BF-200 ALA.

Table 33: Number of patients exposed to PDT-1 and PDT-2 by treatment area - SAF

	Number (%) of patients					
	Placebo N=32		BF-200 ALA N=55		Total N=87	
PDT sessions						
PDT-1	32	(100)	55	(100)	87	(100)
PDT-2	24	(75.0)	21	(38.2)	45	(51.7)
Illumination procedures PDT-1						
Only treatment area A, 1 illumination	17	(53.1)	28	(50.9)	45	(51.7)
Only treatment area A, 2 illuminations	0	(0.0)	4	(7.3)	4	(4.6)
Only treatment area B, 1 illumination	13	(40.6)	18	(32.7)	31	(35.6)
Only treatment area B, 2 illuminations	1	(3.1)	4	(7.3)	5	(5.7)
Treatment areas A and B, 1 illumination	0	(0.0)	0	(0.0)	0	(0.0)
Treatment areas A and B, 2 illuminations	1	(3.1)	1	(1.8)	2	(2.3)
Illumination procedures PDT-2						
Only treatment area A, 1 illumination	14	(43.8)	8	(14.5)	22	(25.3)
Only treatment area A, 2 illuminations	0	(0.0)	2	(3.6)	2	(2.3)
Only treatment area B, 1 illumination	8	(25.0)	8	(14.5)	16	(18.4)
Only treatment area B, 2 illuminations	1	(3.1)	3	(5.5)	4	(4.6)
Treatment areas A and B, 1 illumination	0	(0.0)	0	(0.0)	0	(0.0)
Treatment areas A and B, 2 illuminations	1	(3.1)	0	(0.0)	1	(1.1)

N= number of patients in a treatment group; PDT= photodynamic therapy.
For patients with two illuminations of two treated fields in two different treatment areas it is assumed that field 1 is treated in the first illumination.

The Safety Analysis Set included 384 patients who received BF-200 ALA with PDT and 149 patients who received vehicle with PDT. The study was completed by 96.9% and 87.9% of patients, respectively.

Table 34: Disposition of patients - Safety Analysis Set

	Vehicle		BF-200 ALA	
Safety Analysis Set	**N=149**		**N=384**	
	No. patients	**%**	**No. patients**	**%**
Completed	131	87.9	372	96.9
Discontinued	18	12.1	12	3.1
Adverse event	0	0	2	16.7
Lack of efficacy	2	11.1	0	0
Lost to follow-up	2	11.1	2	16.7
Other	5	27.8	3	25.0
Protocol deviation	0	0	1	8.3
Withdrawal By Subject	9	50.0	4	33.3

Safety Analysis Set: all subjects who received at least one dose of randomized treatment (BF-200 ALA or vehicle/ placebo) irrespective of whether an illumination was performed.

Table 35: Study drug exposure - Safety Analysis Set

		Vehicle		BF-200 ALA	
		N=149		N=384	
		n	%	n	%
Number of PDT sessions, n (%)	One PDT session	23	15.4	201	52.3
	Two PDT sessions	126	84.6	183	47.7
Number of illuminations – PDT1, n (%)	1	112	75.2	288	75.0
	2	37	24.8	95	24.7
	3	0	0	1	0.3
Number of illuminations – PDT2, n (%)	1	99	78.6	148	80.9
	2	27	21.4	34	18.6
	3	0	0	1	0.5
Interruption in any PDT session	Yes	0	0	15	3.9
Any pain-relief measure during PDT 1 or PDT2, n(%)	Yes	15	10.1	107	27.9
Region of skin illuminated	Face (including forehead)	82	55.0	231	60.2
	Bald Scalp	46	30.9	111	28.9
	Face and Bald Scalp	21	14.1	42	10.9
Lamp used for PDT, n (%)	Narrow spectrum lamps, pooled (ca. 630 nm)	87	58.4	212	55.2
	Aktilite® CL 128 (630 nm)	44	50.6	124	58.5
	Omnilux® PDT (633 nm)	11	12.6	35	16.5
	BF-RhodoLED® lamp (635 nm)	32	36.8	53	25.0
	Broad spectrum lamps, pooled	62	41.6	172	44.8
	Waldmann® PDT 1200L (600 to 750 nm)	3	4.8	15	8.7
	Hydrosun®/PhotoDyn® 750 (580 to 1400 nm)	59	95.2	157	91.3

Safety Analysis Set: all subjects who received at least one dose of randomized treatment (BF-200 ALA or placebo/vehicle) irrespective of whether an illumination was performed.

Max: maximum; Min: minimum; n (%): number (%) of patients; PDT: photodynamic therapy

Adverse events

ALA-AK-CT002 follow-up

Of the 570 subjects in the ITT population, 549 completed the clinical treatment phase of the study and entered the follow-up phase (ITTFU population): 68, 241 and 240 from the vehicle, BF-200 ALA and Metvix groups, respectively. Of the 549 patients in the ITTFU, follow-up was completed by 532 (96.9%) patients. AEs during ALA-AK-CT002 follow-up included basal cell carcinoma (1.2%, 1.7%, 0% in theBF-200 ALA, Metvix and vehicle groups, respectively), seborrheic keratosis (1.2%, 1.3%,0%), squamous cell carcinoma of skin (0.4%, 0%, 0%; 0%, 0.4%, 1.5%) resp.), Bowen's disease (0%, 1.3%, 1.5%), skin papilloma (0%, 0%, 1.5%). There was no report of melanoma. AK was reported for 2 subjects in both the BF-200 ALA and Metvix groups. None of these AEs was regarded by the investigator as treatment-related.

ALA-AK-CT003 follow-up

Of the 114 subjects in the FAS population, all 114 completed the clinical treatment phase of the study, and 102 (89.5%) patients completed both the 6-month and 12-month follow-up: 70 in the BF-200 ALA group and 32 in the vehicle group. Overall, 4 subjects (3 in the BF-200 ALA group and 1 in the vehicle group) had a new non-melanoma or *melanoma skin cancers* in the treatment area (face and forehead, bald scalp). Two subjects had a superficial cell carcinoma (in month 6 and 12, both BF-200 ALA) and 2 subjects had a nodular basal cell carcinoma (one BF-200 ALA, one placebo, both in month 6).

ALA-AK-CT005

In a clinical trial (ALA-AK-CT005) designed to investigate the sensitization potential of ALA with 216 healthy subjects, 13 subjects (6%) developed allergic contact dermatitis after continuous exposure for 21 days with doses of ALA that were higher than doses normally used in the treatment of AK. Allergic contact dermatitis has not been observed under regular treatment conditions.

Study ALA-AK-CT006

More TEAEs were observed after application of the ALA gel and subsequent illumination compared to the placebo gel (10 TEAEs in 4 patients vs. 1 TEAE in 1 patient). After application of the ALA gel, 10 TEAEs were observed in 4 of the 12 patients. Seven of the 10 TEAEs occurred in one patient. Seven events were of moderate severity and 3 events were of mild severity. A relationship to the IMP was considered certain for 5 of the 10 events, probable for 3 of the 10 events, possible for 1 of the 10 events, and unlikely for 1 of the 10 events.

The TEAEs considered to have a causal relationship to the ALA gel were 6 local TEAEs (eyelid oedema, swelling face, application site erosion, application site pruritus, and application site pain and feeling hot) and headache.

No deaths and no SAEs occurred. No discontinuations due to an AE were reported. All TEAEs had recovered by the end of the study. No clinically relevant changes in laboratory, vital sign, and ECG parameters between screening and follow-up were observed. Pain and local tolerability assessment revealed pain and skin reactions to occur more often after application of ALA gel compared to the placebo gel. Immediately after PTD treatment following placebo gel application, none of the patients developed pain in the treatment area. After PTD treatment following ALA gel application, all patients developed pain. Most of the patients developed pain of moderate intensity; one patient had pain of severe intensity.

Twenty-four hours after placebo gel application, mild dryness was observed in 8 patients and mild itching was observed in 1 patient. After ALA gel application all patients showed skin reactions of mild or moderate intensity and all investigated skin reactions (erythema, dryness, burning, erosion, oedema, and itching) were observed. The most frequently observed skin reaction was erythema, oedema, and burning. The most frequently moderate skin reaction was erythema. At follow-up, i.e., after a short time span of 7 days, no obvious improvement in skin reactions was observed compared to Period 2 (ALA gel). One Patient showed severe erythema and erosion at follow-up. The healing time was expected to be comparable with the one after first- and second-degree burns, i.e., 14 to 21 days. At the follow-up visit, the investigator assessed the overall tolerability as good in 9 patients, as satisfactory in 1 patient, and as not satisfactory in another patient. These results are in line with the SmPC of ALA. In clinical trials with ALA, local skin reactions at the application site were observed in about 90% of the subjects. The most common signs and symptoms observed were application site irritation, erythema, pain, and oedema which were usually of mild or moderate intensity. They lasted for 1 to 4 days in most cases; in some cases, however, they persisted for 1 to 2 weeks or even longer. Headache is also known to be commonly associated with ALA gel.

ALA-AK-CT007

The overall incidence of TEAEs was higher in the BF-200 ALA group than in the placebo group (100% vs. 68.8%). In both groups, the most commonly reported TEAEs were those of the application site, i.e. application site pain, erythema, pruritus, scab exfoliation, and oedema. The incidences of these TEAEs were higher in the BF-200 ALA group than in the placebo group. Application site pain was the most

common individual TEAE in both groups, reported in 53 (96.4%) patients in the BF-200 ALA group and in 16 (50.0%) patients in the placebo group.

ALA-AK-CT007 follow-up

Of the 84 subjects in the FAS population, 80 subjects completed the clinical treatment phase of the study. Furthermore, 4 patients withdrawn from the clinical phase entered the FU. 80 patients completed the FU phase; all 54 (100%) BF-200 ALA patients and 26 (86.7%) vehicle patients completed both the 6-month and 12-month follow-up). In ALA-AK-CT007 follow-up new lesions in the treated field(s) were observed in 16 patients (29.6%) in the BF-200 ALA group, and 4 lesions (13.3%) in the vehicle group. Of these, 3 were assessed as probably or possibly related. Moreover, the trend for an increase in carcinoma was also observed in ALA-AK-CT007, 6 AEs of neoplasms (2x basal cell carcinoma, 1x Bowen´s disease, 1x keratoacanthoma, 1x squamous cell carcinoma in situ, 1x acrochordon) were observed in the BF-200 ALA group vs. 0 in the placebo group.

Overview of adverse events

Overall, 64.4% (96/149) of patients who received vehicle and 96.6% (371/384) of patients who received BF-200 ALA had one or more AEs.

Table 36: Overview of adverse events - Safety Analysis Set

	Vehicle N=149		BF-200 ALA N=384	
	n	%	n	%
Any TEAE	96	64.4	371	96.6
Related	88	59.1	368	95.8
SAE	4	2.7	9	2.3
Related	0		0	

Safety Analysis Set: all subjects who received at least one dose of randomized treatment (BF-200 ALA or placebo/vehicle) irrespective of whether an illumination was performed.

AE: adverse event; n: number of patients with event; SAE: serious adverse event; TEAE: treatment-emergent AE (AEs from first PDT to 12 weeks after last PDT or discontinuation)

Related: assessed by investigator as at least possibly related to treatment.

Table 37: Incidence of frequently reported TEAEs - Safety Analysis Set

MedDRA System Organ Class Preferred Term	Vehicle N=149		BF-200 ALA N=384	
	n	%	n	%
Any TEAE	96	64.4	371	96.6
General disorders and administration site conditions	87	58.4	367	95.6
Application site discharge	0	0	5	1.3
Application site discomfort	1	0.7	7	1.8
Application site erosion	1	0.7	8	2.1
Application site erythema	57	38.3	321	83.6
Application site exfoliation	6	4.0	61	15.9
Application site hypersensitivity/ hyperalgesia [a]	0	0	10	2.6
Application site induration	0	0	36	9.4
Application site irritation	35	23.5	289	75.3
Application site edema	3	2.0	106	27.6
Application site pain	39	26.2	272	70.8
Application site paresthesia	2	1.3	19	4.9
Application site pruritus	15	10.1	108	28.1
Application site reaction	2	1.3	11	2.9
Application site scab	3	2.0	48	12.5
Application site vesicles	1	0.7	29	7.6
Infections and infestations	7	4.7	40	10.4
Bronchitis	2	1.3	6	1.6
Nasopharyngitis	1	0.7	17	4.4
Onychomycosis	1	0.7	4	1.0
Injury, poisoning and procedural complications	3	2.0	14	3.6
Head injury	1	0.7	4	1.0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	6	4.0	9	2.3
Basal cell carcinoma	2	1.3	4	1.0
Squamous cell carcinoma	2	1.3	1	0.3
Nervous system disorders	3	2.0	14	3.6
Headache	2	1.3	10	2.6
Skin and subcutaneous tissue disorders	9	6.0	38	9.9
Eczema	2	1.3	7	1.8
Erythema	1	0.7	7	1.8
Intertrigo	2	1.3	1	0.3
Pruritus	1	0.7	6	1.6
Skin exfoliation	1	0.7	17	4.4

Safety Analysis Set: all subjects who received at least one dose of randomized treatment (BF-200 ALA or placebo/vehicle) irrespective of whether an illumination was performed.

Frequently reported: incidence of ≥ 1% AEs (preferred term) for any TEAE that occurred through 12 weeks after the last PDT (end of study).

n: number of patients with event; PDT: photodynamic therapy; TEAE: treatment-emergent AE (AEs from first PDT to 12 weeks after last PDT or discontinuation)

[a] "Application site hypersensitivity" was a faulty classification used at at single center in study ALA-AK-CT002. The correct term should have been "application site hyperalgesia" as clarified by the investigator after database lock (see Appendix A.1.2 ALA-AK-CT002).

For treatment-related AEs, one or more related AEs were reported for 88 (59.1%) patients who received vehicle and 368 (95.8%) patients who received BF-200 ALA.

Table 38: Incidence of frequently related TEAEs - Safety Analysis Set

MedDRA System Organ Class Preferred Term	Vehicle		BF-200 ALA	
	N=149		N=384	
	n	%	n	%
Any related TEAE	88	59.1	368	95.8
General disorders and administration site conditions	87	58.4	367	95.6
Application site discharge	0	0	5	1.3
Application site discomfort	1	0.7	7	1.8
Application site erosion	1	0.7	8	2.1
Application site erythema	57	38.3	321	83.6
Application site exfoliation	6	4.0	61	15.9
Application site hypersensitivity/ hyperalgesia [a]	0	0	10	2.6
Application site induration	0	0	36	9.4
Application site irritation	35	23.5	289	75.3
Application site edema	3	2.0	106	27.6
Application site pain	39	26.2	272	70.8
Application site paresthesia	2	1.3	19	4.9
Application site pruritus	15	10.1	107	27.9
Application site reaction	2	1.3	11	2.9
Application site scab	3	2.0	48	12.5
Application site vesicles	1	0.7	29	7.6
Nervous system disorders	1	0.7	8	2.1
Headache	1	0.7	7	1.8
Skin and subcutaneous tissue disorders	3	2.0	27	7.0
Erythema	1	0.7	7	1.8
Pruritus	0	0	6	1.6
Skin exfoliation	1	0.7	17	4.4

Safety Analysis Set: all subjects who received at least one dose of randomized treatment (BF-200 ALA or placebo/vehicle) irrespective of whether an illumination was performed.

Frequently reported: incidence of ≥ 1% related AEs (preferred term) for any related TEAE that occurred through 12 weeks after the last PDT (end of study).

Related: at least possibly related.

PDT: photodynamic therapy; TEAE: treatment-emergent AE (AEs from first PDT to 12 weeks after last PDT or discontinuation) [a] Application site hypersensitivity" was a faulty classification used at a single center in study ALA-AK-CT002. The correct term should have been "application site hyperalgesia" as clarified by the investigator after database lock (see Appendix A.1.2, ALA-AK-CT002).

Analysis of the risk of melanoma and non-melanoma skin cancers

In the pooled placebo group, 3% (4/132) of the patients developed new NMSC in the entire treatment areas (face and scalp), compared to 3.3% (12/366) of the patients in the pooled BF-200 ALA group.

Table 39: Description of the analysis of the risk of melanoma and non-melanoma skin cancers - Study ALA-AK-CT002

CT002	Age	Preferred Term	Location	Day after PDT1/PDT2	CSR	FUP
BF-200 ALA						
	60-69	Seborrhoeic keratosis		84/1	x	
	60-69	Basal cell carcinoma		168/86	x	
	60-69	Seborrhoeic keratosis		168/86	x	x
	60-69	Malignant melanoma	Elbow	19	x	
	70-79	Basal cell carcinoma	Back	171/86	x	

CT002	Age	Preferred Term	Location	Day after PDT1/PDT2	CSR	FUP
BF-200 ALA						
	80-89	Sarcoma		13/-72	x	
	60-69	Basal cell carcinoma	Back	82/1	x	
	60-69	Basal cell carcinoma	Hip	82/1	x	
	70-79	Seborrhoeic keratosis		197	x	x
	60-69	Squamous cell carcinoma		92/8	x	
	70-79	Squamous cell carcinoma of skin	Capillitium	300/219		x
	70-79	Squamous cell carcinoma of skin	Cheek left	300/219		x
	70-79	Seborrhoeic keratosis		221/131	x	x
	70-79	Basal cell carcinoma	Capillitium	1/-81	x	
	70-79	Basal cell carcinoma		165/84		x
Metvix						
	70-79	Haemangioma		24	x	
	60-69	Bowen's disease		273/189		x
	60-69	Basal cell carcinoma		449/365		x
	70-79	Bowen's disease		168/84	x	
	70-79	Skin neoplasm excision (Keratoacanthoma)		148/64	x	
	60-69	Non-Hodgkin's lymphoma stage II		36	x	
	80-89	Seborrhoeic keratosis		264/176	x	x
	60-69	Squamous cell carcinoma		37/-48	x	
	60-69	Squamous cell carcinoma		201/117	x	x
	70-79	Squamous cell carcinoma		157/80	x	
	70-79	Chronic lymphocytic leukaemia (worsening)		129/46	x	
	70-79	Seborrhoeic keratosis		182	x	
	70-79	Seborrhoeic keratosis	Chest	168/84	x	x
	80-89	Keratoacanthoma		26	x	
	70-79	Basal cell carcinoma	Forehead	439/358		x
	70-79	Bowen's disease	Capillitium	330/243		x
	80-89	Basal cell carcinoma	Nose /right	204/117	x	
	60-69	Seborrhoeic keratosis		85/1	x	
	80-89	Basal cell carcinoma	Alar wing of the nose	29/-60	x	
	80-89	Seborrhoeic keratosis		264/176	x	x
	70-79	Basal cell carcinoma	Left ear retroauricular	154/70	x	
	70-79	Basal cell carcinoma	Low leg right	32/-54	x	
	70-79	Basal cell carcinoma	Back	142/57	x	
	70-79	Bowen's disease	Right shoulder	188/99	x	x
	80-89	Basal cell carcinoma	Treatment area	448/321		x
	70-79	Basal cell carcinoma	Ear left	1/-91	x	

CT002	Age	Preferred Term	Location	Day after PDT1/PDT2	CSR	FUP
Placebo						
	70-79	Basal cell carcinoma	Back	53/-39	x	
	80-89	Basal cell carcinoma	Face	22/-63	x	
	80-89	Squamous cell carcinoma		85/1	x	
	70-79	Bowen's disease	Area B (scalp)	318/234		x
	80-89	Bowen's disease		114/30	x	
	70-79	Squamous cell carcinoma	Preauricular left side	173/85	x	x
	60-69	Skin papilloma	Hand right	399/316		x

In the BF-200 ALA group,

- 4 patients (1.6 %) had one or two BCCs, 2 patients (0.8 %) had one or two SCCs, 1 patient (0.4 %) had a melanoma, 1 patient (0.4 %) had a sarcoma, and 4 (1.6 %) patients had a seborrheic keratosis.

In the Metvix group,

- 8 patients (3.3 %) presented with one or two BCCs, 5 patients (2.0 %) with an SCCs or keratoacanthoma, 4 patients (1.6 %) with Bowen's disease, 5 patients (2.0 %) with a seborrheic keratosis, and 3 patients (1.2%) with various other neoplasms.

In the placebo group,

- 2 patients (2.8 %) had a BCC, 2 patients (2.8 %) an SCC, 2 patients (2.8 %) a Bowen's disease, and 1 patient (1.4 %) a skin papilloma.

Together, 4.9 % of the patients in the BF-200 ALA group, 9.8 % of the Metvix patients and 9.7 % of the placebo patients displayed neoplastic lesions.

A melanoma occurred in one patient in the BF-200 ALA group, none in the Metvix or placebo groups. According to the patient's medical history, the patient affected by melanoma in the BF-200 ALA group suffered from 2 melanomas, an acanthoma, an SCC, and a dysplastic naevus syndrome prior to study start, which had been treated previously.

The following neoplasia occurred in patients of study ALA-AK-CT003, either during the clinical phase (CSR) or the follow-up (FUP). Indicated are the patient number and the preferred term (PT):

Table 40: Description of the analysis of the risk of melanoma and non-melanoma skin cancers - Study ALA-AK-CT003

CT003				
BF-200 ALA	**PT**	**Location**	**CSR**	**FUP**
	nodular BCC	Forehead		6m
	SCC*	Forehead		12m
	BCC*	Forehead		6m
Placebo				
	Squamous cell carcinoma	2nd biopsy	End of study	
	nBCC	Forehead		6m

*For two subjects with lesions previously diagnosed as superficial cell carcinoma (in month 6 and 12, both BF-200 ALA 10%) a corrected determination became available after database lock (see study

report ALA-AK-CT003). Diagnosis was stated more precisely as squamous cell carcinoma and basal cell carcinoma, respectively.

In the BF-200 ALA group

- 2 patients (2.6 %) presented with a BCC, 1 patient (1.3 %) with an SCC.

In the placebo group,

- one patient (2.7 %) had a BCC and one patient (2.4 %) an SCC. There was no melanoma. The SCC in the placebo group was identified through the second biopsy taken at the end of the study.

Percent values were calculated using for BF-200 ALA the safety population of 81 patients in the CSR and 77 patients in the FU, and for placebo 41 patients in the CSR and 37 patients in the FU.

Again, based on the number of patients with neoplasia (together 3.1% in the BF-200 ALA group and 5.1% in the placebo group) there is no indication for an increased risk of neoplasia after ALA PDT.

The following neoplasia occurred in patients of study ALA-AK-CT007, either during the clinical phase (CSR) or the follow-up (FUP).:

Table 41: Description of the analysis of the risk of melanoma and non-melanoma skin cancers - Study ALA-AK-CT007

CT007				
Treatment	**Lesion**	**Location**	**Rel Day PDT1/2**	**Source**
BF-200 ALA	Bowen`s	Treatment Area	454	FU
BF-200 ALA	BCC	Treatment Area	113	FU
Placebo	Seborrhoeic keratosis	Left chest	169/85	CSR
BF-200 ALA	Seborrhoeic keratosis	Worsening Right Hip	167/83	CSR
BF-200 ALA	SCC	Treatment Area	246/164	FU
BF-200 ALA	BCC	Cervix	301/206	FU
BF-200 ALA	BCC	Shoulder left	-11/-106	CSR
BF-200 ALA	Keratoacanthoma	Left lower leg	149	FU/CSR
BF-200 ALA	Acrochordon	Axillar both sides	101	FU/CSR

In summary, in the BF-200 ALA group

- there were 2 patients with one or two BCCs (3.7 %), 2 SCC or keratocanthoma (3.7 %), 1 seborrhoeic keratosis (1.8 %) and 1 Bowen's disease patient (1.8 %). In one patient an acorchordon (1.8 %) was observed which is a harmless small benign tumor.

In the placebo group, which was about half the size of the verum group,

- only one case of seborrheic keratosis (3.1 %) was observed.

One BCC at the shoulder of a patient in the ALA group was already present prior to PDT. There was no melanoma in either group.

Percent values were calculated using for BF-200 ALA the safety population of 55 patients in the CSR and 54 patients in the FU, and for placebo 32 patients in the CSR and 30 patients in the FU.

The total percentage of neoplasia was 18.3 % in the BF-200 ALA group (16.5 % without the BCC that was present already before PDT) and 3.1 % in the placebo group,

Pooled analysis
In the pooled analysis, only 1/366 patients in the BF-200 ALA group, 0/247 patients in the Metvix group and 0/132 patients in the placebo group presented with a malignant melanoma during the follow-up phase of the studies.

Serious adverse event/deaths/other significant events
No serious adverse events or deaths observed during the clinical trials were considered drug related. In the SOC General disorders and administration site conditions, severe AEs were reported for 1.3% (2/149) of patients who received vehicle and 36.7% (141/384) of patients who received BF-200 ALA.

Table 42: Incidence of frequently reported severe TEAEs - Safety Analysis Set

MedDRA System Organ Class Preferred Term	Vehicle N=149		BF-200 ALA N=384	
	n	%	n	%
General disorders and administration site conditions	2	1.3	141	36.7
Application site erythema	1	0.7	58	15.1
Application site exfoliation	0	0	6	1.6
Application site irritation	0	0	82	21.4
Application site edema	0	0	4	1.0
Application site pain	1	0.7	97	25.3
Application site paresthesia	0	0	9	2.3
Application site pruritus	0	0	5	1.3
Application site scab	0	0	7	1.8

Safety Analysis Set: all subjects who received at least one dose of randomized treatment (BF-200 ALA or placebo/vehicle) irrespective of whether an illumination was performed.

Frequently reported: incidence of ≥ 1% AEs (preferred term) for any severe TEAE that occurred through 12 weeks after the last PDT (end of study).

n: number of patients with event; PDT: photodynamic therapy; TEAE: treatment-emergent AE (AEs from first PDT to 12 weeks after last PDT or discontinuation); Source: ISS Table 3.4

There was no death in the Phase I/II clinical program, including study ALA-AK-CT005, study ALA-AK-CT001 and study ALA-AK-CT006. In the Phase III program, no death was reported in study ALA-AK-CT002, study ALA-AK-CT003, or study ALA-AK-CT007. One death was reported in the context of the Phase III study ALA-AK-CT002 but was determined to be unrelated to the study drug.

Laboratory findings
Hematology, biochemistry, and urinalysis data gave no indication for any drug-related changes (laboratory values over time, individual subject changes, and individual clinically significant abnormalities).

Discontinuation due to adverse events
There was no AE that led to discontinuation in ALA-AK-CT003 or ALA-AK-CT007. In ALA-AK-CT002, one patient had AEs of application site pain and application site irritation on Day 1 that led to discontinuation and were assessed as definitely related to treatment. Illumination stopped one minute after start because of the severe application site pain and irritation (burning).

Post marketing experience

There have been no safety signals from post-marketing sources. Since marketing in the EU early in 2012 approx. 91.000 patients have been treated with BF-200 ALA gel. No spontaneous cases concerning melanoma or new NMSCs have been reported to the MAH.

2.5.1. Discussion on clinical safety

In study ALA-AK-CT007, BF-200 ALA was well tolerated. The safety profile was consistent with the AK overall population which includes mainly elderly patients and similar characteristics of the underlying disease. The most commonly reported TEAEs (also the most commonly reported related TEAEs) were the TEAEs of the application site (application site pain, erythema, pruritus, scab exfoliation, and oedema). The frequency of serious TEAEs was very low and no related serious TEAEs were reported. Local skin reactions were mainly of mild to moderate intensity. In the BF-200 ALA group, the incidences shifted to less severe and more mild TEAEs rated as discomfort during and after PDT-2 compared with PDT-1. In the placebo group, no conclusion can be drawn due to low number of patients who had PDT-2. In the ALA-AK-CT007 follow up study, safety analyses in the FU showed that treatment of AK lesions with BF-200 ALA is well tolerated. The overall lesion status in the treatment areas revealed comparable skin disease progression over the FU period in both treatment groups.

In ALA-AK-CT002 follow-up, there was a marginal increased risk for basal cell carcinoma (BCC) and AK in the verum group; in ALA-AK-CT003 follow up overall, 4 subjects (3 in the BF-200 ALA group and 1 in the vehicle group) had a new non-melanoma or melanoma skin cancers in the treatment area (face and forehead, bald scalp). Two subjects in the BF-200 ALA group had a "superficial cell carcinoma" and 2 subjects (one each for BF-200 ALA and placebo group) had a nodular basal cell carcinoma. In ALA-AK-CT007 follow-up, a trend for an increase in carcinoma was also observed in ALA-AK-CT007, 6 AEs of neoplasms (2x basal cell carcinoma, 1x Bowen´s disease, 1x keratoacanthoma, 1xsquamous cell carcinoma in situ, 1x acrochordon/fibroma molle) were observed in the BF-200 ALA group vs. 0 in the placebo group. According to the results of the follow up studies of ALA-AK-CT002, ALA-AK-CT003, ALA-AK-CT007, there seems to be a slight increase in the rate for non-melanoma skin cancer, including basal cell carcinoma (BCC) and carcinomata in situ respectively.

There is no evidence that patients in the BF-200 ALA group had an increased ratio of neoplasia. Furthermore, there is no apparent pattern in the time of onset of neoplasia after PDT that may point towards a causal relationship.

Percent values were calculated using for BF-200 ALA the safety population of 248 patients in the CSR and 241 patients in the FU, for Metvix 247 patients in the CSR and 240 in the FU, and for placebo 76 patients in the CSR and 68 patients in the FU.

In study ALA-AK-CT-007, it appears that a difference in the percentage of patients treated with ALA- and placebo that have neoplasia potentially may exist. However, since in study ALA-AK-CT007 all lesions were followed separately and the location of new lesions was well documented, it can be stated that none of the lesions were in the treated field (the region actually treated with BF-200 ALA) and only 3 lesions (one Bowen's, one BCC, one SCC) were in the respective treatment area (either face/forehead or scalp).

During the assessment, the PRAC concluded to delete nasopharyngitis from the list of safety concerns. The rationale for not listing nasopharyngitis as related AE and deleting it from the SmPC is as follows:

- The frequency of nasopharyngitis was not increased in patients treated with PDT compared to the general population. Most patients complained of nasopharyngitis or bronchitis during the fall and winter, the typical season for these infections. No patient reported of repeated infections in the course of the study.

- Most of the cases were reported several weeks after PDT. Considering the late onset of the infections observed after the last PDT in both verum-treatment groups (ALA-AKCT002), the high incidences reported for nasopharyngitis especially in the elderly target population and the coincidence with the typical seasonal pattern, it was assumed that these AEs were highly unlikely to be induced by PDT treatment.

- None of the reported cases of nasopharyngitis were serious and all patients recovered,

- Nasopharyngitis is a self-limited disease.

BF-200 ALA has been marketed in the EU since the beginning of 2012. No spontaneous safety cases related to nasopharyngitis have been reported and no cases are described in the literature. Also, no cases of nasopharyngitis have been rated as likely related or related in the clinical study ALA-AK-CT007. Therefore, nasopharyngitis has been deleted in Section 4.8 of the updated. The PIL has been updated accordingly.

2.5.2. Conclusions on clinical safety

Overall, the safety of BF-200 ALA appears to be acceptable and also well tolerated in the photodynamic treatment of AK lesions on face and scalp with AK lesions located within 1-2 treatment fields of an overall size of an area of approximately 20 cm^2. There were no unexpected safety concerns reported and most common ADRs were as expected, transient local skin reactions.

2.5.3. PSUR cycle

The PSUR cycle remains unchanged.

The next data lock point will be 14 June 2018.

2.6. Risk management plan

The MAH did not update the RMP during the procedure as this proposed extension of the indication is not a significant change in the product's indication for use and does not lead to a significant change to the risk-benefit balance, since the disease area is similar, the treated age group remains unchanged, and the proposed treatment population is not materially different from the current. The MAH proposed to provide an updated RMP with the response to questions (RTQ) for the renewal of the MA (EMEA/H/C/002204/R/0023), waited by 16 August 2016, which was considered acceptable by the PRAC rapporteur.

The CHMP endorsed this advice without changes.

2.7. Update of the Product information

As a consequence of this new indication to include treatment of actinic keratosis of mild to moderate severity on the face and scalp (Olsen grade 1 to 2) and of field cancerization, sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC have been updated. The Package Leaflet has been updated accordingly.

In addition, the Marketing authorisation holder (MAH) took the opportunity to make minor editorial changes in the SmPC and Package Leaflet and to bring section 6.6 of the SmPC in line with the latest QRD template.

2.7.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package

leaflet has been submitted by the applicant and has been found acceptable for the following reasons: The additional information in the SmPC does not substantially change to the PL or the readability of the PL.

3. Benefit-Risk Balance

Benefits

Beneficial effects

The clinical efficacy of BF-200 ALA nanoemulsion gel for PDT in study ALA-AK-CT007 in subjects with AK target lesions of mild to moderate intensity (AK grade 1 and 2 according to Olsen et al. 1991) within 1-2 treatment fields (overall size of approximately 20 cm^2) in the treatment area of the face and forehead or bald scalp (excluding eyes, nostrils, ears, and mouth). Ameluz was superior to vehicle with respect to patient complete clearance rates (90.9% vs. 21.9% for Ameluz and placebo, respectively; $p < 0.0001$) and lesion complete clearance rates (94.3% vs. 32.9%, respectively; $p < 0.0001$), as controlled 12 weeks after the last PDT. 96.9% of patients with AK on the face or forehead were cleared from all lesions, 81.8% of patients with AK on the scalp were totally cleared. Lesions of mild severity were cleared by 99.1% vs. 49.2%, those of moderate intensity by 91.7% vs. 24.1% for treatment with Ameluz or placebo, respectively. After only 1 PDT complete patient clearance resulted in 61.8% vs. 9.4%, and complete lesion clearance in 84.2% vs. 22.0% for Ameluz or placebo treatment, respectively. Clinical efficacy was maintained during the follow-up periods of 6 and 12 months after the last photodynamic therapy. After Ameluz treatment, 6.2% of the lesions were recurrent after 6 and additionally 2.9% after 12 months, respectively (placebo: 1.9% after 6 and additionally 0% after 12 months, respectively).

The efficacy data from the pooled analysis supported the overall efficacy in the single study outcome. Generally, the effects of BF-200 ALA on all efficacy variables were consistent in all analyses of subgroup populations stratified by age, sex, lamp type, skin type, AK lesion severity, number of AK lesions at baseline, and AK lesion area.

Follow up data of the Phase III studies ALA-AK-CT002, ALA-AK-CT003 and ALA-AKCT007 demonstrated that the efficacy achieved 12 weeks after the last PDT was highly maintained during a 12-month follow up period. In study ALA-AK-CT002, recurrence rates were slightly lower than those achieved with MAL in all subgroups. Moreover, as demonstrated in study ALA-AK-CT007 with field-directed treatment skin quality improved continuously from baseline to FU2.

Uncertainty in the knowledge about the beneficial effects

Patient and lesion recurrence rates were in favor for the vehicle in all follow up studies. In study ALA-AK-CT002 follow up, at 12 months follow-up in subjects that had been classified as complete responders 12 weeks after the last PDT and that were still cleared (free of lesions) after 6 months follow-up in the BF-200 ALA group 14.7% of the lesions were reported to be recurrent compared to 11.4% in the placebo group. For study ALA-AK-CT003 follow up, during a 12-month follow-up period, 15% of the lesions after were recurrent after treatment with PDT and BF-200 ALA group compared to 8.8% in the placebo group. For study ALA-AK-CT007 follow up, patient recurrence rates were 24.5 % and 14.3 % after 6 months, and additionally 12.2 % and 0 % after 12 months for Ameluz and placebo, respectively. However, it appears that overall treatment taking into consideration the study period as well as the follow up period, there is a lack of statistical significance between the incidence of skin neoplasia between BF-200 ALA and placebo in all studies. In many cases, the lesions appeared in areas that had not been previously treated with BF-200 ALA.

Risks

Unfavourable effects

In study ALA-AK-CT007, the safety profile was consistent with other studies. The most commonly reported TEAEs were application site pain, erythema, pruritus, scab exfoliation, and oedema. The frequency of serious TEAEs was very low and no related serious TEAEs were reported. Local skin reactions were mainly of mild to moderate intensity. Safety analyses in the FU period showed that treatment of AK lesions with BF-200 ALA was well tolerated.

No serious adverse events or deaths observed during the clinical trials were considered drug related. Hematology, biochemistry, and urinalysis data gave no indication for any drug-related changes (laboratory values over time, individual subject changes, and individual clinically significant abnormalities).

Uncertainty in the knowledge about the unfavourable effects

For listing of the important identified risks, important potential risks and missing information, see RMP.

According to the results of the follow up studies of ALA-AK-CT002, ALA-AK-CT003, ALA-AK-CT007 there seems to be an increased rate for (non)melanoma skin cancer, including basal cell carcinoma (BCC) and carcinoma in situ respectively. However, no clear causality between the risk and the treatment has been identified. The safety concerns will be closely monitored within the pharmacovigilance program from the MAH.

Effects Table

Table 1. Effects Table for Ameluz (data cut-off: 03-SEP-2014)

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
Favourable Effects						
Ameluz was statistically significantly more effective than placebo and comparator, Effective treatment of non-melanoma cancer (AK) Good long-term tolerance Good cosmetic outcome Most TEAEs related to local tolerability at the application site and well known Negligible systemic absorption of ALA		N/A	Actinic keratosis/ field canceri-zation	Metvix and placebo	(Slightly) increased rate for (non)melanoma skin cancer, including basal cell carcinoma (BCC) and carcinomata in situ respectively. Patient and lesion recurrence rates were in favor for the vehicle in all follow up studies.	ALA-AK-CT002/-003 follow up -/ ALA-AK-CT007 including follow up studies, ALA-AK-CT005, ALA-AK-CT006
Unfavourable Effects						
More Side effects of narrow spectrum Illumination with regard to local tolerability at the application site (e. g. erythema) More pronounced than those observed with broad-spectrum lamps.		N/A	See above	See above		ALA-AK-CT002/-003/-007 including follow up studies, ALA-AK-CT005, ALA-AK-CT006

Benefit-Risk Balance

Importance of favourable and unfavourable effects
BF-200 ALA was evaluated for PDT in adult subjects with AK lesions of mild to moderate severity on the face and/or scalp or with *field cancerization.* The efficacy results of the Phase III pivotal studies show a consistent and robust benefit with regard to the percentages of subjects with total AK lesion clearance and the total clearance of individual AK lesions compared to the vehicle control. In terms of safety, no new ADRs or safety concerns have been identified in study ALA-AK-CT007. The treatment is considered well tolerated and transient local skin reactions are manageable.

Benefit-risk balance
The CHMP is of the opinion that the benefit observed with Ameluz in terms of clearance of mild and moderate severity AK lesions in the field treatment area of cancerisation outweigh the known safety risks. Therefore, the benefit-risk is considered positive.

Discussion on the Benefit-Risk Balance

The efficacy of BF-200 ALA nanoemulsion gel is considered demonstrated for PDT in adult subjects with AK lesions on the face and/or scalp and can be applied to field cancerization containing multiple AKs. The efficacy results of the Phase III pivotal studies are consistent and robust with regard to the superiority of BF-200 ALA over vehicle for both the percentages of subjects with total AK lesion clearance and the total clearance of individual AK lesion. Narrow-spectrum wavelength illumination yielded better results with regard to subject total AK lesion clearance which was associated with an increased incidence of local skin reactions and pain. These adverse reactions were, however, non-serious and self-limiting with duration of up to 7 days in most patients. However, irrespective of the illumination source, the efficacy of BF-200 ALA was generally superior to the other treatments. In addition, the cosmetic outcome of this combination has been proven in a Phase III study with field therapy.

In conclusion, BF-200 ALA in combination with red light seems an appropriate therapeutic option for PDT in subjects with AK lesions on the face and scalp. It can be applied in *field-directed* PDT and overcomes disadvantages of presently available preparations concerning stability of ALA and absorption to the lesions. Overall BF-200 ALA appears to be rather safe and well tolerated in the photodynamic therapy of AK lesions on face and scalp with the exception of expected transient local skin reactions.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation accepted		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of Indication to include treatment of actinic keratosis of mild to moderate severity on the face and scalp (Olsen grade 1 to 2) and of field cancerization based on the phase III clinical study ALA-

AK-CT007. As a consequence, sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC are updated. Package Leaflet is updated accordingly. In addition, the Marketing authorisation holder (MAH) took the opportunity to make minor editorial changes in the SmPC and Package Leaflet and to bring section 6.6 of the SmPC in line with the latest QRD template.

The variation leads to amendments to the Summary of Product Characteristics and Package Leaflet.